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ATLAS AND EPITOME

OF

GENERAL PATHOLOGIC HISTOLOGY

BY

DOCENT DR. HERMANN DÜRCK
OF THE PATHOLOGIC INSTITUTE, MUNICH

AUTHORIZED TRANSLATION FROM THE GERMAN

EDITED BY

LUDVIG HEKTOEN, M.D.
PROFESSOR OF PATHOLOGY IN RUSH MEDICAL COLLEGE, CHICAGO

With 176 Colored Illustrations on 80 Lithographic Plates and 36 Figures in Black and Colors

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1904

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EDITOR'S PREFACE.

I HAVE compared the translation with the original text, and I believe that the translation satisfactorily answers its purpose. All notes or additions made by me are enclosed in brackets [ ]. It is a pleasure to recommend this book to the English-speaking student of Pathology, because I feel sure that it will prove even more useful than the two volumes on Special Pathologic Histology.

LUDVIG HEKTOEN.

OCTOBER 1, 1904.

72782

AUTHOR'S PREFACE.

The saying that without a thorough knowledge of histologic processes it is impossible to penetrate the mysteries of pathologic alterations applies with special force to general pathology. It is only by a painstaking study of the minute changes in the elementary building-stones of the organism that the ability to associate definite conceptions with the technical terms of general pathology is acquired.

In this very matter of terminology a regretable laxity is but too frequently observed. Such words as "inflammation," "degeneration," "necrosis," and the like are constantly employed without any direct mental association with the microscopic changes observed in the cellular constituents of the body and when these changes do not in the least justify the use of the respective term.

It is true that the interpretation of pathologic processes has undergone very great changes in the course of time since Virchow's monumental creation of cellular pathology, and at the present day there still exists a wide divergence of opinion even in regard to fundamental matters; but thanks to the untiring efforts of investigators during the past decades, especially along experimental lines, our conceptions have gained very much in scope and definiteness. The plan of this "Atlas (and Epitome") obviously forbids an exhaustive, critical presentation of diverging views, although for many reasons we cannot help acknowledging that they are quite justifiable. I have, therefore, in most cases contented myself with giving the generally accepted views in regard to the significance of pathologic processes, and have only cursorily referred to mere theories, whether old or new, believing that it is more to the learner's advantage to be supplied with as true and objective a representation as possible of pathologic processes in general, than to have a number of different and conflicting theories expounded.

It is evident from the nature of the subject that the volume on general pathologic histology is the proper place for the full discussion of morbid growths; for any attempt to give a description of even the principal forms of neoplasms occurring in individual organs in the special portion of this work would have necessitated countless repetitions. I merely wish to emphasize this point once more because of the criticism from various quarters that the subject of tumors is too briefly treated in the special portion.

An effort has been made to render the present general portion practically independent of its companion volume, in order to enlarge as much as possible its individual value to the student of pathologic histology.

In this, as in the two preceding volumes, all the illustrations have been made from original specimens, without combining different microscopic fields. An experienced eye will not fail to detect in most of the plates and in the illustrations reproduced by photo-chemical methods a certain advance in technic and a striving after perfection. To the artist, Mr. K. Dirr, who executed most of the original illustrations in this edition (with the exception of thirty plates from the pencil of Mr. Krapf, the (official) artist of the University, I am greatly indebted for the extraordinary care and fidelity with which he has accomplished his task. The art lithographer, Mr. C. Reichhold, of Munich, has accomplished the difficult feat of reproducing the very complicated and delicate original paintings by the rapid process of lithographic printing with as many as twenty-six colors, in a way that closely approaches the effect of the original water colors, and, I believe, has never been surpassed by this method of reproduction. My warmest thanks are due to this firm.

But more than to any one else I am indebted to Mr. J. F. Lehmann, the publisher, for the many sacrifices he has made to insure for the present volume the best possible equipment in the matter of illustrations.

In bringing the "Atlas and Epitome of General Pathologic Histology" before the public I venture to hope that the book will prove itself a useful guide to the study of pathologic histology, and perhaps suggest new subjects for investigation in the same field.

HERMANN DÜRCK.

GARGNANO ON LAKE GARDA.

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GENERAL
PATHOLOGIC HISTOLOGY.

I. CIRCULATORY DISTURBANCES.

HEMORRHAGE.

THERE are two ways in which the cellular elements of the blood may escape from the vascular system, either by solution of continuity or by passage of the blood-cells through the intact walls of smaller vessels. In the former case there is a laceration of the vessels, and the expression *hemorrhage per rhexin* is employed; or, if the injury to the vessel is worked by some caustic substance, attacking the wall from without, or by inflammatory processes, the term *hemorrhage per diabrosin* is also employed.

The blood-corpuscles may, however, pass through an apparently intact vascular wall in the absence of any gross injury, and the hemorrhage resulting in this way is known as a *hemorrhage by diapedesis.* Such a hemorrhage, it is true, never occurs under normal conditions; it requires for its production, first, a heightening of the blood-pressure, and, second, an increase in the permeability of the wall. Diapedesis is in general observed only in thin-walled vessels—in capillaries, small veins, and possibly very small arteries. The permeability of the vessel-wall and consequent occurrence of diapedesis may be favored by a variety of factors. These factors may be mechanical, thermic, or chemic in nature; it is well known that a certain group of poisons have an especially injurious effect upon vascular walls, which is followed by the escape of the elements of the blood. The most important of these poisons is phosphorus; but mercury, platinum, and antimony are also capable of injuring the walls of blood-vessels in this way. The toxic metabolic products of many micro-organisms have a similar injurious effect on vessels. Hemorrhage by diapedesis may be induced experimentally and its various stages may be observed directly under the microscope, the best tissue for this purpose being the mesentery of a frog, as Cohnheim first showed in his studies of this process. If the vein is ligated or the return flow of the blood obstructed by distorting or bruising the vessel, the movement of the blood-column in the venous and capillary vessels is seen to be retarded (Fig. I.). The vessels become distended, the so-called marginal zone of plasma, which is ordinarily present, disappears, and its position is occupied by a closely packed mass of red corpuscles. If the obstruction to the return flow continues, then the movement of the blood is arrested gradually, stasis occurs, the red blood-cells become closely aggregated, and may be pressed against one another so densely that their outlines almost or quite disappear. Following this, individual red blood-corpuscles are gradually seen to make their way through the wall of the vessel. At certain places on the outside of a capillary a small nodular swelling appears and gradually becomes larger; this corresponds to part of a red blood-cell. At a certain stage of the phenomenon half the blood-cell is seen on the inner side and the other half on the outer side of the wall, which constricts the cell in the middle; gradually the inner half also passes through the wall, and the extravasated corpuscle, by virtue of its elasticity, at once regains its original shape. It was formerly believed (Arnold) that the corpuscles escaped through special preformed openings—so-called stigmata or stomata; but these supposed openings were later found to be nothing more or less than local accumulations of cement substance between the cells; increase in blood-pressure and injuries to the wall cause gaping at these points and permit the corpuscles to escape. In the case of the red blood-cells, however, the escape from the vessel is never an active process, since they are entirely devoid of the ameboid movement characteristic of the leukocytes; they therefore remain quite passive and are simply forced through the wall.

Hemorrhage by diapedesis under certain conditions may affect a considerable portion of the blood-vessel, the extravasated blood surrounding the vessel like a mantle. When the diapedesis is protracted, the accumulation of blood may be considerable; indeed, fatal extravasations may result, as in hemorrhage by diapedesis in the gastro-intestinal canal in cirrhosis of the liver.

Whatever the mode of escape, when the blood has entered the perivascular tissue it fills all the surrounding spaces and cavities—*i. e., hemorrhagic infiltration* of the tissue results. If the hemorrhage continues, the tissue becomes densely packed with the blood-corpuscles and the resulting pressure leads to local death of tissue, or necrosis; in this way is produced hemorrhagic infarction, which will be referred to again later on. Delicate tissues may be destroyed at once by the pressure of the escaping blood, the elements being completely disintegrated, which, for instance, is the rule in the brain.

What is the fate of the blood after its escape from the vessel? Of course, it cannot remain unaltered in the more or less damaged tissue, but undergoes a series of changes, both morphologic and chemic, which ultimately lead to its absorption. There is no doubt that part of the extravasated blood is at once taken up by the surrounding lymph-vessels, especially the perivascular lymphatic sheaths. Accordingly, it is common after hemorrhage to find a deposition of red blood-cells in the nearest lymph-glands, where these cells then undergo further disintegration. If the mass of blood is very great and has entered a preformed cavity, or a cavity formed by destruction or displacement of tissue, coagulation takes place in the extravasated blood, just as in the stagnating blood after death. Fibrin is formed, and the blood-cells are lumped to form coherent masses—the so-called cruor coagula [currant-jelly clots.—Ed.]. The process of coagulation

PLATE I.

FIG. 1.—**Multiple Capillary Hemorrhages in the Cerebrum** (Hemat.-eosin. × 270.): 1, Cerebral substance; 2, engorged capillaries; 3, small artery with hemorrhagic infiltration of its walls; 4, hemorrhage by diapedesis in the tissues around a small artery; 5, smaller hemorrhagic foci without any connection with any blood-vessel visible in the section.

FIG. 2.—**Hemorrhagic Destruction of the Tissue of a Lymphatic Gland in a Hemorrhagic Bubo from a Case of Plague** (Hemat.-eosin. × 67.): 1, Intact gland tissue infiltrated with many red blood-cells; 2, blood-vessels showing great engorgement; 3, completely disintegrated and necrotic gland tissue, almost completely displaced by red blood-cells.

FIGURE I.

Hemorrhage by Diapedesis from a Small Vein in the Distended Mesentery of the Frog (× 200.): 1, Vein filled with closely packed blood-cells; 2, red blood-cells in the act of passing through the wall; 3, red blood-cells that have extravasated and collected in the surrounding connective tissue; 4, red blood-cells in a state of beginning disintegration; 5, blood-platelets; 6, leukocytes; 7, chromatophores.

FIGURE II. (Text p. 52.)

Atrophy of Subepicardial Fatty Tissue in Senile Atrophy of the Heart (× 300.): 1, Connective-tissue fibers; 2, atrophic fatty cells containing several smaller fat-droplets instead of a single large drop; 3, blood-vessels; 4, former fat-cell reduced to a narrow spindle cell.

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depends on the appearance of a fibrinogenetic substance in the presence of a ferment. The former is evidently liberated as the tissue-cells or leukocytes die, and the formation of fibrin threads may be studied directly under the microscope; they first appear as radiating or brush-like figures, the individual threads of which converge toward certain definite points. These points are usually blood-plates or leukocytes, or the remains of fixed cells, and have been designated by Hauser "coagulation centers." The blood-plates themselves are merely the products of the disintegration of red blood-cells, being formed by the

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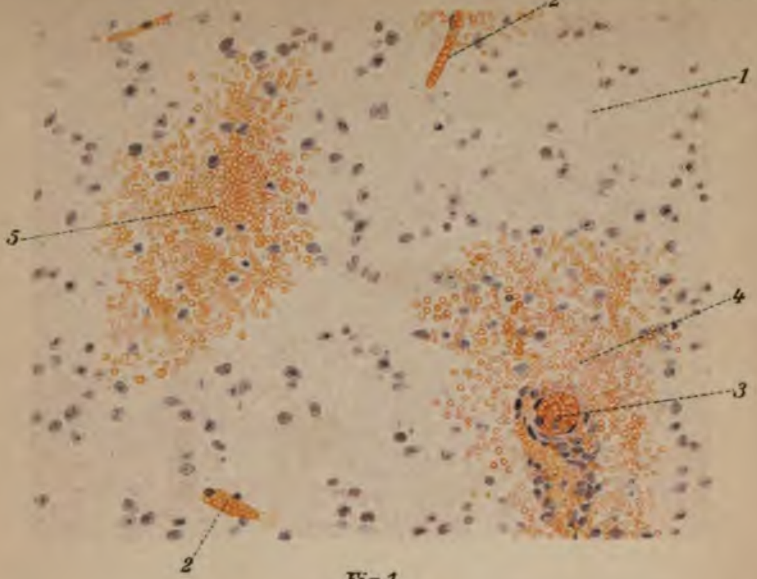

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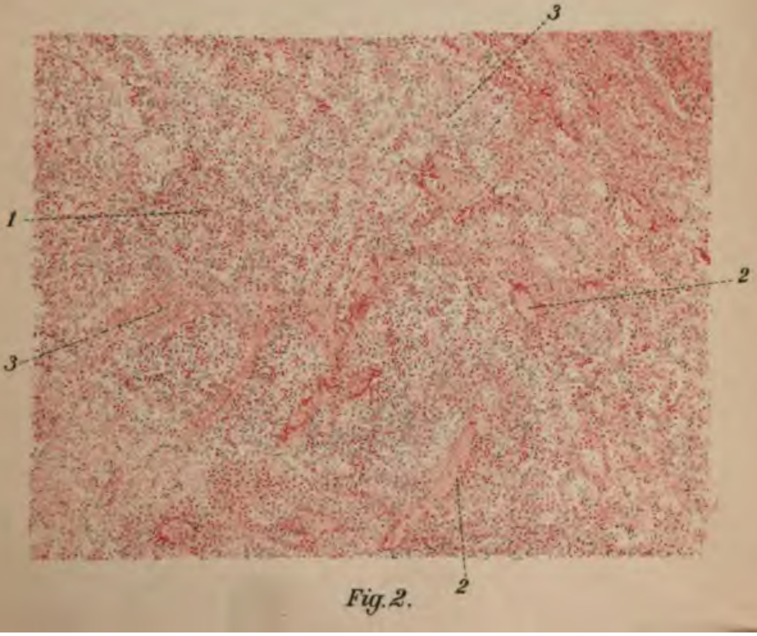

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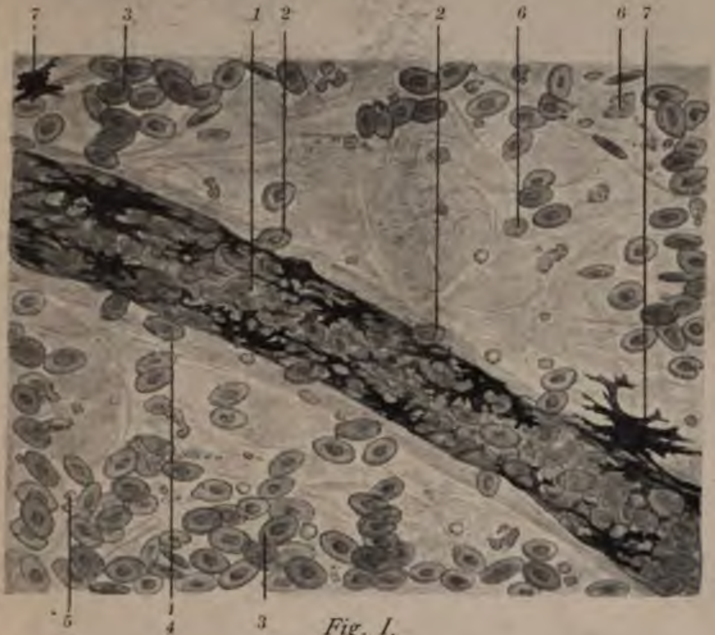
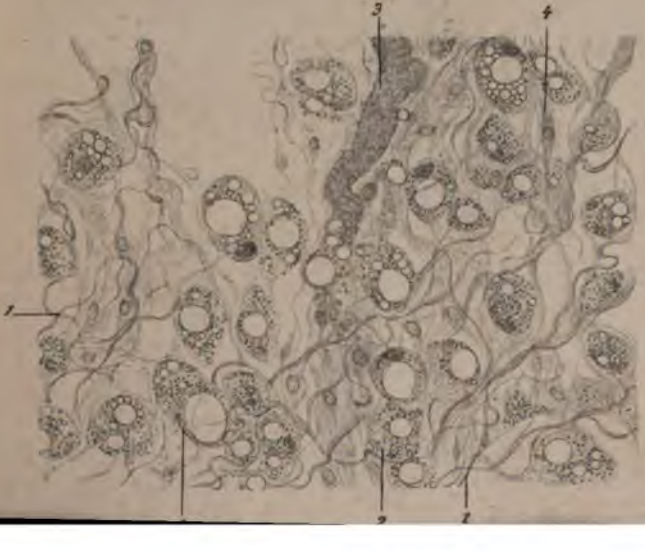


Fig. I.



processes known as *plasmorrhexis* and *plasmoschisis*. These processes also, consisting in the breaking-up of red blood-cells into small spheric fragments—blood-platelets—may occasionally be studied directly under the microscope during a hemorrhage by diapedesis in the mesentery of the frog. When first formed, the fibrin is granular; the granules are then arranged into threads and trabeculæ which form a network, in the meshes of which the blood-cells are inclosed. The fate of these coagula will be described in greater detail later in connection with thrombosis. The red corpuscles scattered through the tissue at once proceed to lose their hemoglobin until all trace of the pigment has disappeared. The hemoglobin is taken up by the streams of plasma which traverse the tissue, and this at first leads to a diffuse brownish imbibition in the immediate neighborhood of the hemorrhage. The corpuscles, of course, become paler and paler, until at last they are mere colorless stromas and cease to take acid anilin stains, such as eosin, orange, or Congo-red, stains that impart a bright-red color to intact erythrocytes. As the red cells lose their color they also undergo distinct swelling, the two pit-like depressions disappear, the discs are gradually converted into spheres which are wholly colorless, and when closely aggregated, they become flattened by mutual pressure into a mosaic. Soon, however, a diametrically different process shows itself: the swollen, spheric stromas begin to shrink, numerous minute retractions appear on the periphery, which in the optic section frequently appear as minute lenticular bodies. These are the so-called "peripheral corpuscles" first described by Ecker and Virchow. The colorless stromas may remain a long time in the tissue at this stage; in the end, however, they become completely disintegrated or dissolved; or the contraction continues, the cells presenting deep, pit-like retractions or assuming various shapes like a rubber ball that has been compressed in different directions. Some of the extravasated blood-cells, however, are early taken up by wandering cells; this occurs to a varying extent in the different organs. These wandering cells are chiefly lymphocytes, perhaps also derivatives of fixed tissue-cells, and on account of their faculty of taking corpuscular elements of all kinds into themselves and adapting their own bodies to the needs of these particles, they have been designated by von Recklinghausen contractile cells [phagocytes.—Ed.]. We shall meet these cells frequently and in a variety of rôles in pathologic processes. In the present case these contractile cells become loaded with red corpuscles, often to such an extent that the nucleus of the cell is almost completely obscured. The erythrocytes taken up by these cells undergo contraction, while the hemoglobin at the same time becomes inspissated. Since the latter is not washed out, as in the case of extracellular erythrocytes, the contraction of the inclosing cell is accompanied by the formation of irregular, pointed and angular granules, which in the end cannot be distinguished from fragments of coloring-matter.

Meanwhile an important change takes place in the diffused hemoglobin which has infiltrated the surrounding tissue, in that the iron in the hemoglobin becomes less firmly bound. Although it contains iron, normal hemoglobin does not give the usual microchemic reactions for iron with potassium ferrocyanid and hydrochloric acid (Perls) and sulphate of ammonium (Quincke); as the iron becomes less firmly bound there is a distinct, positive reaction, which shows itself in the production of Prussian blue or black iron sulphid. This modification of the hemoglobin was first designated *hemosiderin* by Neumann. At first it infiltrates the tissue; soon, however, it tends to accumulate at certain points, and always within so-called contractile [phagocytic.—Ed.] cells. The latter at first stain a uniform blue or black when the iron test is applied; later the diffuse infiltration of the tissue disappears entirely and only the cells contain large and small fragments and granules of hemosiderin. The erythrocytes, which have been inclosed in the contractile cells from the beginning, also undergo a similar chemic transformation, so that the shrunken remnants at a certain stage also contain hemosiderin granules. But the splitting-off of the iron continues; the metal disappears more and more, and, as it disappears, the microchemic reaction changes, so that the application of ferrocyanid and hydrochloric acid no longer produces a pure blue color; on the other hand, the constantly increasing accentuation of the yellowish-brown color of the pigment itself gives rise to a more greenish color, until finally the iron disappears altogether and the test turns out entirely negative. When this stage has been reached, the blood-pigment is entirely free from iron and is called *hematoidin*, which is regarded as identical with the bilirubin of bile. Concurrently with the splitting-off of the iron the contractile cells which contain the pigment-granules disintegrate by a fatty degeneration of their protoplasm, and the granules eventually come to lie free in the tissue; part of the iron-free hematoidin is converted into crystalline structures—the so-called hematoidin crystals—in the form of rhombic plates and needles. Virchow, in his epochal work on pathologic pigments, stated that these crystals were not derived from a fluid medium, but were produced by a gradual conversion of granules. We shall have occasion to return once more to the discussion of hemosiderin as well as hematoidin in connection with pathologic pigments.

It is needless to say that this metamorphosis in extravasated blood is not uniform in every portion of the extravasation; the larger the latter, the longer will it take for complete conversion and absorption. As the process goes on the tissue destroyed by the hemorrhage is displaced by newly formed connective tissue, or, in other words, by the formation of scar tissue, a process which belongs to the domain of pathologic regeneration and will, therefore, be described in that section.

THROMBOSIS.

It has just been shown that the blood, after its escape from the vessels into the tissue or into large body-cavities, undergoes a process of coagulation. After death also, when stagnation of the blood takes place, or when blood is taken from the living body and poured into a vessel, it becomes converted after a time into a semisolid mass or lump; in other words, it undergoes the same process of coagulation. The coagulated masses of blood found in cadavers, in the heart, and in the large venous trunks are of various kinds: either they represent dark-red bodies, so-called masses of cruor, or pale, yellowish white, ribbon-shaped, tough, elastic formations, so-called chicken-fat or goose-fat clots, also called briefly fibrin clots. It is obvious that the differences in postmortem clots are to be attributed to differences in their component parts. If the entire mass of blood in a vessel or in one of the chambers of the heart coagulates rapidly after death, a red clot or "cruor-clot" [currant-jelly clot.—Ed.] results; if, on the other hand, the red blood-cells have time, before coagulation takes place, to gravitate to the bottom, leukocytes and fibrinogen only take part in the process, which, therefore, results in the production of a colorless, chicken-fat clot. When blood is taken from the living body and allowed to stand in a vessel, the entire mass is usually converted into a body resembling a cruor-clot, the so-called blood-cake. But when fresh blood, after it has been removed from the body, is beaten up or whipped in a vessel with a hard body, the latter becomes coated with a stringy substance resembling a white clot and consisting chiefly of colorless masses of fibrin.

Under certain conditions coagulation of blood or some of the constituents of blood may take place also during life within the circulatory system, and this process is known as thrombosis. The most important factors for the occurrence of thrombosis are retardation of the blood-current, changes in the wall of the vessels and of the heart, and, finally, under certain conditions, changes in the chemic composition of the blood itself. If a blood-vessel is ligated in two places, the contents coagulate between the two ligatures and the thrombus is, of course, composed of all the constituents of the contained blood. A thrombus produced in this way is dark red, and if it is examined soon after its formation, it will be found to be traversed by threads of fibrin arranged in radiating lines and issuing from the endothelium of the blood-vessel. In small vessels these fibrin threads may be packed so closely as to fill the entire lumen with a network formed by the union of radiating fibers, in the meshes of which both red and white blood-corpuscles are inclosed. The fibrin threads, as may be readily recognized in the peripheral portions of the thrombus, are attached to, and radiate from, endothelial cells, both such as are *in situ* and cells that have been cast off from the vessel-wall. The bodies of the cells are sometimes found in a state of disintegration; sometimes the oval nuclei only are visible, or these may be undergoing dissolution (Plate 4, Fig. I.). Hauser, who was the first to call attention to these coagulation centers, believed that the injury to the blood-vessel wall incident to ligation caused the death of the endothelial cells; that this was followed by the liberation of fibrin ferment, which at once combined with the fibrinogen and caused the precipitation of fibrin threads. But disintegrating endothelial cells are not the only elements capable of producing this fibrin ferment: it results much more frequently and in much greater quantities from the formation of the so-called blood-platelets.

The blood-platelets [or plates.—Ed.] were first described by Hayem as *hematoblasts*. In 1882 Bizzozero also regarded them as a preformed third constituent of the blood, present in the normal circulation, a view which has recently been shared by Deetjen, who believes that he has found nuclei in the platelets and that he has observed ameboid movements. [These investigations have been extended in this country by Pratt, who *also* believes that there exists a third preformed element in the blood, distinct from the fragmentary extrusions from red corpuscles that take part in coagulation.—Ed.] On the other hand, Löwit and others advance the theory that the blood-platelets are the result of precipitation of globulins in the blood, while a number of other authors incline to the opinion that the platelets merely represent disintegration products of white, and especially of red, blood-cells (Ziegler, Arnold). As has been mentioned in connection

PLATE 2.

FIG. 1.—**Marantic White Thrombus from the Right Auricle** (Hemat.-eosin. × 66.): 1, Heart muscle; 2, network of fibrin threads, including leukocytes in close apposition with the heart muscle; 3, masses of blood-platelets; 4, larger collection of leukocytes.

FIG. 2.—**Advanced Stage of Organization in a Venous Thrombus** (Hemat.; orange. × 66.): 1, Adventitia with vasa vasorum; 2, media, inner layer; 3, longitudinal muscle bundles of the wall of the vein in transverse section; 4, newly formed blood-vessels that have grown into the wall of the vein from the adventitia; 5, young, growing masses of connective tissue and endothelium entering the thrombus.

PLATE 3.

FIG. 1.—**Organization of a Venous Thrombus** (Hemat.-eosin. × 250.): 1, Muscular layer of the wall of the vein; 2, blood-pigment deposited in the wall of the vein; 3, young endothelial sprouts, for the most part already filled with recently deposited red blood-cells, and growing in toward the thrombus.

FIG. 2.—**Contracted Organized Mural Thrombus of the Aorta** (Hemat.-eosin. × 64.): 1, Adventitia; 2, media; 3, former position of the adventitia, indissolubly connected with—4, connective tissue with an excess of tensely stretched fibers, due to the organization of the thrombus, with few nuclei; 5, distended blood-vessel in the newly formed connective tissue.

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with the study of diapedesis in the mesentery of the frog, the extravasated red blood-cells present certain peculiar phenomena of disintegration, plasmoschisis or erythrocytoschisis (Fig. I.). The red blood-cells, after their escape from the circulation, break up into small spheric structures which must be regarded as fragments of erythrocytes; the same process of fragmentation may occur in blood stagnating within the vessels, or even, under certain circumstances, in circulating blood, when the red blood-cells have been injured by some change in the wall, especially in the intima, or by the introduction of foreign bodies into the circulation—such a change, for instance, as may be effected by the artificial introduction of a thread or a bristle. In preparations obtained experimentally and observed in the recent state or fixed immediately after death, the injured

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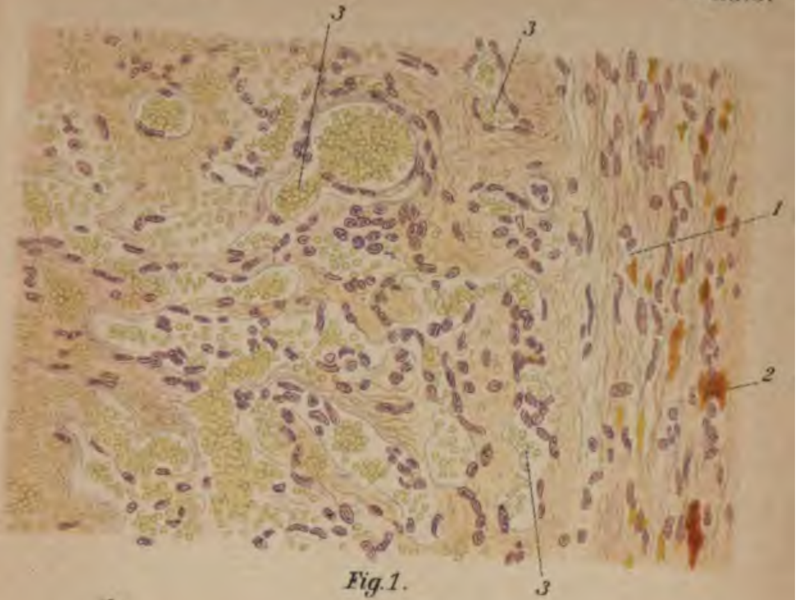

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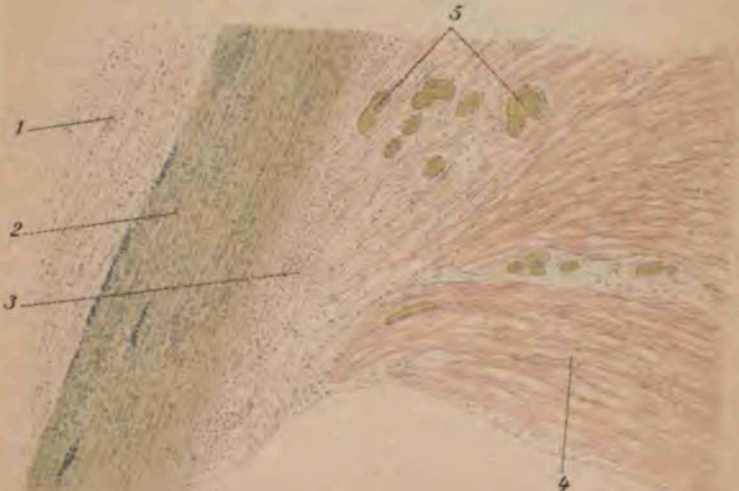

Fig.2.

portions of the blood-vessel wall, as well as the foreign body that has been introduced, are covered with a quantity of small platelets and spheric bodies, which are due to the disintegration of red blood-cells and are at first partially colored with hemoglobin, but soon lose their pigment.

Very soon after death or after the formation of these red blood-cell derivatives a peculiar, *viscous metamorphosis* takes place which results in the formation of closely packed, very finely granular or homogeneous masses. Accordingly, the human cadaver under ordinary conditions never contains well-preserved blood-platelets, as these are always converted into a uniform, slightly granular, or homogeneous mass, faintly tingible with acid anilin dyes. The platelets form one of the most important constituents of coagula formed during life—*i. e.*, of thrombi. It is evident that they may also contribute greatly to the production of fibrin ferment, and platelets, therefore, frequently represent the crystallization centers or the first attraction spheres in commencing precipitation of fibrin. Inflammatory tissue—as, for example, in lungs with pneumonic infiltration, in purulent meningitis, in mucous membranes affected with diphtheria and croup—presents within the vessels of the parts immediately contiguous to the inflammatory foci large numbers of very minute, delicately formed, stellate masses of fibrin, which adhere not only to endothelial cells, either *in situ* or separated from the vessel-wall, but may also contain a very minute central spheric body, which does not take stains in the same way as fibrin, and which is, in fact, a blood-platelet. Sometimes these stellate figures combine to form larger networks, and whenever more robust fibrin threads are formed, the latter again become attraction spheres for the sprouting of new threads of fibrin, and the network thus becomes more and more dense (see Plate 4, Fig. 1). If as the result of a violent injury to the red blood-cells in the blood-current the cells undergo extensive disintegration and large quantities of red blood-platelets are formed at one time, then the resulting, pronounced action of ferment leads to the formation of large masses

PLATE 4.

FIG. 1.—**Beginning Thrombosis in a Small Artery, from a Case of Purulent Fibrinous Leptomeningitis** (Alum cochineal; Weigert's stain. × 625.): 1, Endothelium; 2, muscle-cells in transverse section; 3, muscle-cells in oblique section; 4, cells of the adventitia; 5, leukocytes within the lumen; 6, fibrin stars.

FIG. 2.—**Organized and Partly Canalized Thrombus of the Brachial Artery** (Hemat.; orcein. × 32.): 1, Adventitia; 2, tunica media; 3, organized thrombus—*i. e.*, replaced by connective tissue; 4, newly formed and in part dilated vessels within the thrombus; 5, disintegrated remains of the old thrombus.

PLATE 5.

FIG. 1.—**Recent Red Thrombus from the Crural Vein** (Carmin; Weigert's fibrin stain. × 16.); 1, Masses of fibrin arranged in a circular manner at the periphery, and in the form of single, rib-like strands in the interior portions of the thrombus; 2, closely aggregated red blood-cells; 3, scattered leukocytes; 4, masses of platelets.

FIG. 2.—**Blood Platelet Thrombus** (Carmin; Weigert's fibrin stain. × 280.): 1, Erythrocytes; 2, leukocytes; 3, fibrin; 4, blood-platelets.

FIG. 3.—**Recent Red Venous Thrombus** (Carmin; Weigert's fibrin stain. × 280.): 1, Erythrocytes; 2, leukocytes; 3, fibrin.

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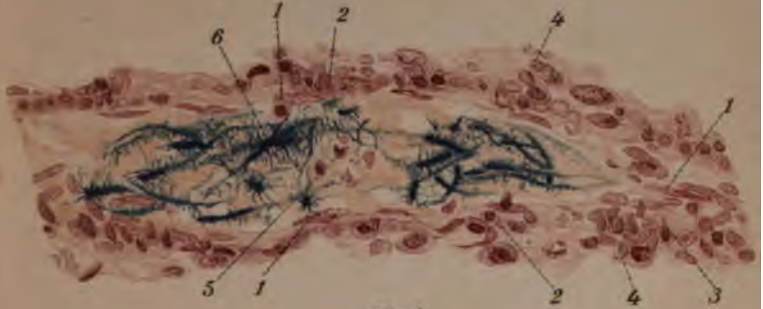
of fibrin; the threads and trabeculæ of the masses of fibrin are usually arranged in concentric circles adherent to the inner wall of the vessel, because the action of the ferment is most intense at this point, as the disintegration of erythrocytes usually begins at the blood-vessel wall (Plate 5, Fig. 1). [Recently it has been shown that red corpuscles may be agglutinated *in vivo* by toxic substances produced by certain bacteria—*e. g.*, typhoid bacilli and by immune cytolytic and hemolytic serums. It is thought that such "agglutination thrombi" may be the primary cause of occlusion of vessels in infectious diseases, such as typhoid fever, and in intoxications like puerperal eclampsia.—ED.]

Disintegrating leukocytes may also produce ferment and thus become coagulation centers. The first impetus to the formation of a thrombus is, therefore, always found

Tab.4



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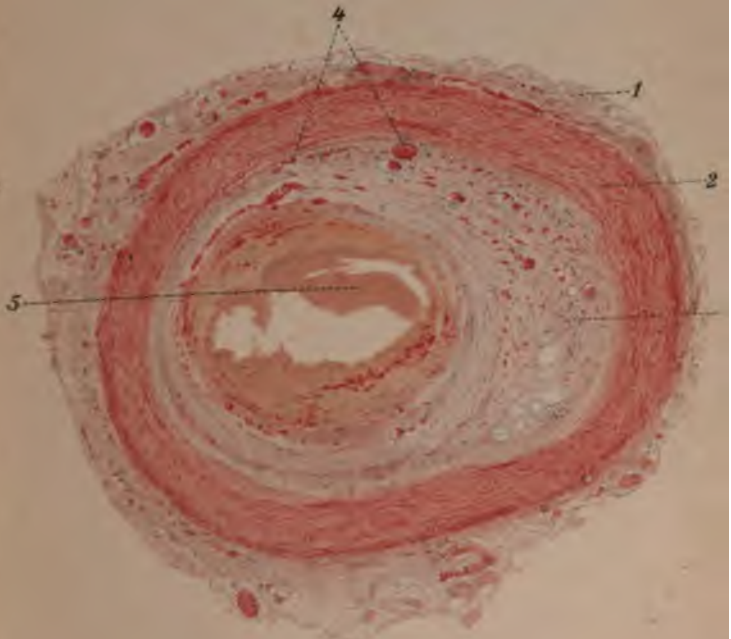

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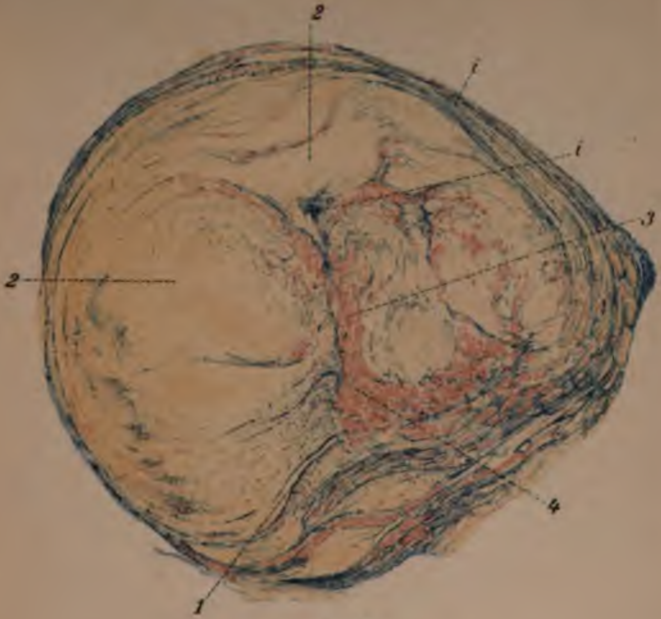

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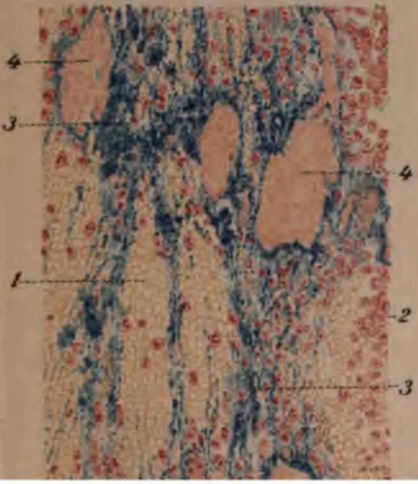
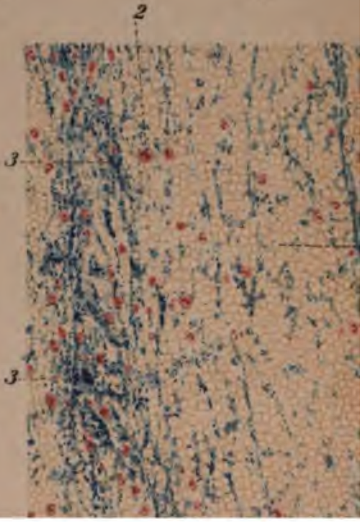




in some degenerative process, beginning either in the vessel-wall or in the cellular constituents of the blood. The greater the number of red blood-cells inclosed in the meshwork of fibrin, the more closely will the clot approach the type of the *red thrombus;* but if the coagulation does not take place rapidly and uniformly throughout the entire lumen of the vessel, the intact red blood-cells may slip down past the masses of fibrin and red blood-platelets, and the growth of the thrombus may be affected chiefly by the agglutination of new masses of platelets and the deposition of additional fibrin threads; the thrombus in such a case contains practically no erythrocytes, and in this way the so-called *white thrombi* are formed. Most commonly, however, thrombotic deposits in transverse section present alternating paler and darker layers, as the number of red blood-cells inclosed in the meshwork during the growth of a clot varies from time to time. Frequently the surface of thrombi in large venous vessels, and especially in the heart, presents rib-like prominences or ridges, separated by moderately deep, groove-like depressions. When a thrombus of this kind is examined, it is found to contain a kind of framework of broad, homogeneous, and colored trabeculæ and bands, winding through the thrombus in an irregular fashion and ending in the rib-like projections on the surface. These structures represent agglutinated masses of platelets, separated from one another by a certain distance and connected by festoons of fibrin. The latter pass in graceful curves from one cord of platelets to another, and are usually most abundant in the immediate vicinity of the platelets, while midway between two cords of platelets the fibrin is more scanty. In addition, however, a white thrombus always contains leukocytes in extremely variable numbers. As a rule, the part of the thrombus nearest the wall of the vessel or heart, as the case may be, contains the greatest aggregation of leukocytes, while their numbers diminish more and more toward the central portion of the thrombus. The number of leukocytes is evidently due in part to the same causes as those which lead to the production of the thrombus itself. If the latter is due to inflammatory processes, especially of a bacterial nature, which have attacked the vessel-wall, the greatest accumulation of leukocytes is found near the vessel-wall and in the microscopic picture of the thrombus they may actually predominate over the platelets and the fibrin. In the beginning they usually are well preserved and present a distinctly tingible cell-body, with the typical lobulated, clover-leaf, horseshoe- or biscuit-shaped nuclei. Later they undergo fatty degeneration, the cell-bodies become loaded with numerous small droplets of fat, and the nuclei disintegrate more and more. As a result the thrombus becomes soft, sometimes semifluid, and almost like pus—it is said to undergo *puriform softening.* The process is not a true suppuration, however, for the leukocytes undergo a kind of fatty degeneration which subsequently involves the layers of fibrin also, so that the latter, as well as the masses of platelets, are converted into a finely granular detritus, containing numberless minute fat-droplets. Occasionally micro-organisms are found in the interior of thrombi, especially when they have been the cause of the thrombus formation, as is often the case in inflammatory processes.

So-called *compression thrombus* is explained chiefly by injury to the vessel-wall from compression by exudates, tumors, ligatures, and the like. The production of so-called *marantic thrombi* is usually explained by an excessive disintegration of the cellular constituents of the blood which occurs in various cachectic conditions and leads to an increased fermentative activity which may go on to a veritable ferment intoxication, while the situation of the thrombus is determined by concomitant local circulatory disturbances.

When a thrombus remains for some time within the living body, it, of course, cannot escape certain changes; in fact, it undergoes a series of metamorphoses which in the main belong to the domain of pathologic organization and may eventually end in spontaneous cure, and sometimes even in a partial restoration of the original circulatory conditions. It has already been mentioned that a thrombus may undergo fatty degeneration and a kind of purulent softening, and after the fatty masses of detritus have been absorbed, it is conceivable that the permeability of the vessel might be restored. What is more frequent, however, is a gradual substitution of the constituents of the thrombus by true fibrous connective tissue, growing from the wall of the vessel, which undergoes a cicatricial contraction and thus may eventually form a cavity resembling the lumen of a blood-vessel. The endothelium of a thrombosed vessel, unless it has undergone alteration from the beginning or has been destroyed and thus given the first impetus to the formation of a thrombus, may undergo proliferation. New cells are formed and grow toward the thrombus. Much importance has been attached to this primary proliferation of the endothelium as regards the subsequent processes that take place, but it seems frequently to be only a temporary stage and to disappear again later. In many cases the proliferated endothelium is probably itself capable of producing connective tissue by a splitting-up of its cells into fibers. The thrombus, then, like any other foreign body, begins to irritate its immediate neighborhood, with the result that newly formed cells from the surrounding connective tissue gradually enter the thrombus. Masses of young cells grow in a perpendicular direction toward the former lumen of the blood-vessel; in the case of the larger vessels they originate in the endothelium, in the connective tissue of the intima, in the subendothelial tissue, and in the vasa vasorum of the adventitia; in the smaller vessels, from the contiguous tissue. Young budding blood-vessels perforate the avascular tunica media in various places, and, accompanied by cords of young, spindle-shaped connective-tissue cells—so-called fibroblasts—and small aggregations of round-cells, destroy the continuity of the muscularis if the vessel is provided with such a layer. Gradually this cellular material makes its way through the middle layer, invades the intima, and, as the endothelium by this time usually presents many interruptions of its continuity, approaches the thrombus and gradually sends out small, budding blood-vessels into the latter from all directions. The vascular buds at first represent thin, cylindric, solid cords of endothelial cells, which at once begin to ramify and surround the periphery of the thrombus with a veritable network of vessel-forming cells. The endothelial cells separate more and more, leaving a narrow capillary lumen which red blood-cells enter in throngs from the vasa vasorum or from other blood-vessels near by. At this stage the red blood-cells that have recently entered the blood-vessels are, as a rule, readily distinguished from the erythrocytes belonging to the thrombus, both by their greater tingibility and their more regular outline. The erythrocytes of the thrombus itself at the same time undergo pigmentary metamorphosis, which runs exactly the same course as has been described above in connection with extravasated blood. At the same time wandering, contractile cells [phagocytes. —Ed.] carry parts of the pigment with them and deposit it in the surrounding tissue; even before this, the hemoglobin may deposit itself by diffusion in the walls of the thrombosed vessel or in the surrounding tissue. It is the rule, therefore, after a time, when the process of organization begins in thrombi which contain red blood-cells, to find fragments of pigment outside of the thrombus itself (Plate 3, Figs. 1, 2).

Part of the cellular material which enters the thrombus, at least in the case of the larger vessels, is, therefore, derived from the intima, or more exactly from the subendothelial connective tissue and from the endothelium itself, while another part is probably contributed by the adventitia. While the cells are still forcing their way through the inner portions of the thrombus, the newly formed connective tissue, in the peripheral portions, with many thin-walled and comparatively wide vessels, is gradually converted into adult fibrous tissue. As the connective-tissue fibers increase, the protoplasmic bodies of the invading fibroblasts, which are at first quite extensive, shrink, their nuclei become smaller and darker, short and spindle-shaped; some of the vessels are obliterated, their walls are pressed together, and their endothelial cells are lost in the surrounding fibrous tissue or themselves contribute to the fibrous formation. At the same time the newly formed blood-vessels in the central portion of the thrombus continue to grow and furnish the means for the advancing absorption of the thrombus in the form of numerous colorless blood-cells which escape through their walls, are converted into contractile cells, become loaded with pigment and other detritus, and then convey their load to the outside. After the thrombotic material has been completely replaced, the newly formed tissue that has grown in from the outside along the entire length of the thrombus may undergo considerable contraction. If the original thrombus did not occlude the entire lumen of the vessel, as in the case of so-called parietal or mural thrombi, the circulation in the vessel, of course, is never entirely interrupted, and organization of the thrombus is usually followed only by a more or less extensive thickening of the wall, in the form of a pad-like deposit on the intima, with which it is inseparably connected. Even in the case of thrombi that completely obliterate the vessel the secondary contraction of the connective tissue may be great enough to form a partial opening of the lumen and in part restore its patency. This result is also chiefly due to contraction of the connective tissue, as fully formed fibrous cicatricial tissue everywhere in the body takes up less space than the original granulation tissue from which it is derived. The patulous portion of the lumen, which in arteries is central, and in veins peripheral, with respect to the thrombus, may permit the entrance of blood into the tissue-spaces formed during the process of contraction, provided the blood is under adequate pressure. Anastomosis between the original lumen and the larger vessels in the new tissue which have escaped the contraction may also be effected, and in this way the entire length of the plug may be traversed by cavities filled with blood and accessible to the circulation—in a word, the thrombus is said to become *canalized.* Sometimes the invading connective tissue leads to the formation of peculiar bands of tissue, which either span the former, lumen-like bridges, or form hard, ridge-like deposits, and sometimes result in bending or kinking of the vessel and in various distortions of the lumen. Such changes are especially apt to occur in thin-walled veins and are often found years after the thrombosis occurred (*endophlebitis deformans*). In rarer cases a continuous concentric contraction of the connective tissue and of the vessel-wall which is closely adherent to it takes place, so that the process eventually leads to the production of compact cylinders which permanently cut off the lumen from the circulation. Ultimately the fibrous tissue becomes hard and poor in nuclei, and calcium salts may be deposited in it, forming concrements which are designated *arterioliths* or *phleboliths*, according to the kind of vessel in which they are found.

The cases in which the thrombus contains not only normal constituents of blood, but also the causes of inflammation, usually bacterial, deserve a brief special discussion. Thrombi of this nature may be either primary or secondary. When primary, they are due to the lodgment of micro-organisms, or parts of thrombi containing micro-organisms, upon some point of the intima the injury to which leads to the deposition of larger plugs. Secondary thrombi are due to the extension of extravascular inflammatory processes, as, for example, in erysipelas or phlegmon of the skin, to the walls of the blood-vessel in the region attacked, thus causing changes in the vascular walls and invasion of micro-organisms from without. Such cases are described by the term *thromboarteritis* or *thrombophlebitis*. The thrombi in these cases are distinguished from the beginning by the extraordinary quantity of white blood-cells with fragmented nuclei which they contain. The intima is usually covered with a wreath of leukocytes, with micro-organisms, as, for example, streptococci, in the uterine vessels in cases of puerperal sepsis. The leukocytes then traverse the vessel-wall from within outward, and collect in every portion of the wall, as well as in the surrounding tissue, where they form dense accumulations, so that the vessel-wall may undergo a true suppuration, rendering it impossible either microscopically or macroscopically to delimit it from the thrombus, on the one hand, and the purulent perivascular infiltration, on the other. Produced in this way, purulent thrombi containing bacteria very often form the starting-point for extension of the mycotic process to the rest of the body by the separation of portions of the thrombi which are carried toward the heart in the case of veins, and to the periphery of the corresponding vascular regions in case of arteries (see under Embolism). If the process is not followed by the death of the individual, and if the vessel-wall has not been entirely destroyed, organization may take place even in these cases after the death of the bacteria and the fatty degeneration of the leukocytes. The process of organization begins in the surrounding connective tissue and its vessels, and proceeds in exactly the same way as in a simple thrombus, except that, owing to the greater destruction of the walls, secondary canalization with restoration of the circulation is less apt to take place, and the corresponding vessel, owing to the cicatricial contraction, usually remains permanently excluded from the circulation.

EMBOLISM.

When foreign corpuscular elements enter the circulation they lodge at some point in the vascular system, either because they are too large to pass the smaller vessels, especially the capillaries; or because, owing to viscid consistence, they become adherent at some point to the vessel-wall; or because they give rise to injury of the delicate intima and attach themselves to the injured spot; or, finally, because they produce alterations, deposits, and coagulations of the constituents of the blood, which in turn become fixed at some narrow portion of the vessels. In every case of this kind the foreign body is designated an *embolus* (from ἐμβάλλειν = to throw in), and the process itself is known as *embolism*. If it is followed by complete occlusion of a vascular territory and the death

PLATE 6.

Fig. 1.—**Micrococcal Embolism of the Kidneys in Pyemia** (Alum-cochineal; Gram. × 500.): 1, Uriniferous tubules; 2, glomerulus; 3, accumulations of staphylococci in the vascular coils of the glomerulus.

Fig. 2.—**Embolic Abscess in the Myocardium in Ulcerative Endocarditis** (Hemat.-eosin.; Gram. × 67.): 1, Myocardium; 2, closely packed blood-corpuscles; 3, mass of staphylococci at the center of the abscess.

of the corresponding region, it is also known as *infarction*, and the affected tissue is designated an *infarct*. The arrested embolus in many cases, of course, leads to the secondary deposition of blood constituents, as described in connection with thrombosis, and we then have, in contradistinction to the original or primary (*autochthonous*) thrombus, an *embolic thrombus*. Emboli most commonly consist of portions of thrombi. When a thrombus undergoes the puriform degeneration or suppuration described in the foregoing, it is obvious that portions of it may readily be torn loose and carried farther along into the circulation. In their subsequent progress they follow the laws of the circulation of the blood; but, owing to retrograde movement of the blood-stream in certain pathologic conditions, as well as to patulence of the foramen ovale between the auricles of the heart, emboli sometimes travel in ways that at first sight may be difficult to explain; such emboli are called *paradoxic*.

Thrombi situated in the heart itself are apt to become the source of embolism, thrombi in the right heart sending their emboli into the lungs, while those in the left ventricle and auricle send out emboli into the greater circulation. Only the smallest corpuscular elements are able to pass through the pulmonary circulation, in that case again entering the left side of the heart, and usually lodging somewhere in the smaller capillary region of the aortic system. Not infrequently particles of recent endocarditic vegetations form the nuclei of embolic thrombi.

As in the majority of cases these particles are loaded

Tab.6

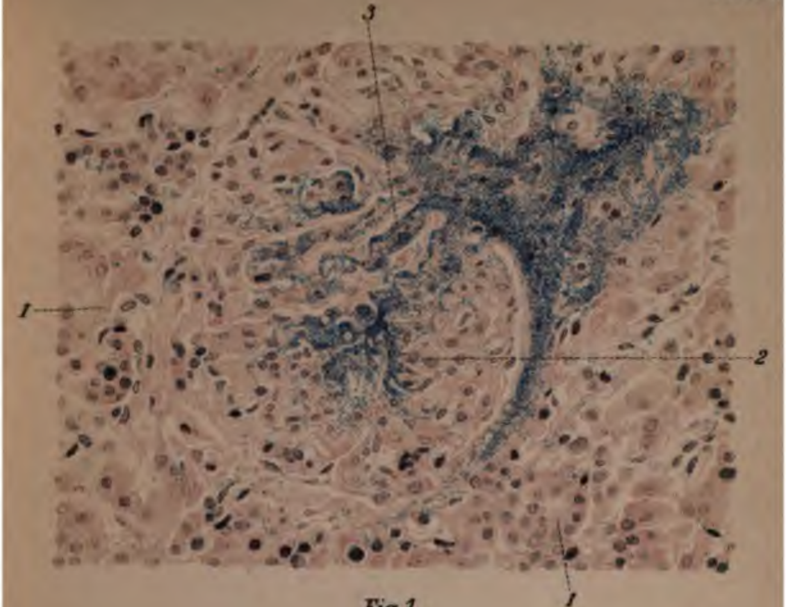
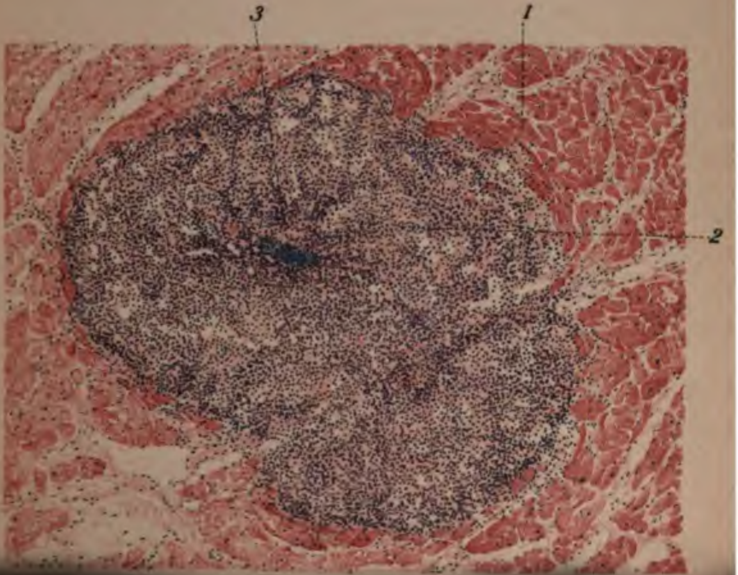


Fig.1.



with bacteria that are capable of causing inflammation, this event may rapidly lead to the extension of mycotic processes in the body. Shreds of altered intima, torn away by the destructive processes in the vascular wall in atheroma, may be washed into the circulation and lodge, according to their size, in vessels of varying caliber. As the roughness of the inner wall of the vessels in atheroma and arteriosclerosis frequently leads to thrombotic deposits, the danger of embolism in the presence of these changes is twofold.

A special form of embolism, which is practically confined to vessels of the smallest caliber—that is, to the capillaries of the larger circulation—is caused by the formation of so-called *ferment thrombi.* It has been stated in connection with thrombosis that certain poisons effect an increase in the fibrin ferment by causing greater disintegration of the morphologic elements of the blood; an increased formation of platelets, particularly, may lead to increased fermentative activity. This occurs in certain forms of poisoning—as, for instance, with corrosive sublimate, arsenic, phosphorus—and after disturbances that suddenly affect a large part of the blood, as evidently occurs in extensive burns. In such conditions it is not uncommon to find numerous emboli in the capillary regions of the kidney and of the brain.

A number of embolic processes are due to cells, either normal constituents of parenchymatous organs or constituents of certain tissues engaged in excessive proliferation, such as tumors; in the former case the term **parenchymatous cell embolism** is used, and various forms of this variety are distinguished, according to the source from which the embolus is derived.

Liver-cell Embolism.—This form is either traumatic, or develops in connection with toxic and infectious diseases. Traumatic liver-cell embolism follows concussion, wounding, laceration, or contusion of the liver tissue, but its extent is not by any means always proportionate to the severity of the hepatic lesion; for while very slight lacerations of the liver are often followed by an extensive

PLATE 7.

FIG. 1.—**Fat-embolism in Fracture of the Thigh** (Stained with sudan III. × 78.): 1, Large sausage-shaped masses of fat in the pulmonary arteries; 2, fat in the capillaries of the alveoli; 3, coal-pigment.

FIG. 2.—**Carcinomatous Embolus in a Branch of the Portal Vein of the Liver, in Primary Carcinoma of the Stomach:** 1, Vessel-wall; 2, large tumor cells; 3, multinuclear tumor cells.

FIG. 3.—**Liver-cell Embolism in a Hepatic Vein in Eclampsia** (Hemat.-eosin. × 78.): 1, Wall of the vein; 2, liver-cells washed in among the red blood-cells.

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flooding of the circulation with liver-cells, embolism may be entirely absent after the most severe and destructive injury to the organ, although life may continue for some time. The liver-cells that have been torn from their seat between the trabeculæ are found first in the hepatic veins, which they enter either through the capillaries or by passing directly from venous vessels that have been opened. The characteristic cuboid liver-cells, which have suffered very little change in their outline, are then found in the midst of the red and white blood-cells; later they are also found in the heart, in the pulmonary arteries and capillaries, and sometimes in the branches of the hepatic and renal arteries; in the two latter cases they have, of course, been transported through a patulous foramen ovale (paradoxic parenchymatous cell embolism). Many forms of hepatic disease, liver abscess, necrotic foci, puerperal eclampsia, and general diseases that lead to parenchymatous changes in the entire liver, as, for example, scarlatina, may lead to the formation of liver-cell emboli by loosening the trabecular framework (dissociation, Browicz) and by bringing about changes in the capillary vessels.

These cells never undergo active proliferation; they lie passive where they have been deposited, without reacting, although occasionally they may form the nucleus for depositions from blood; they may be found unchanged after weeks and months.

A second form of parenchymatous cell embolism is the

Tab. 7.

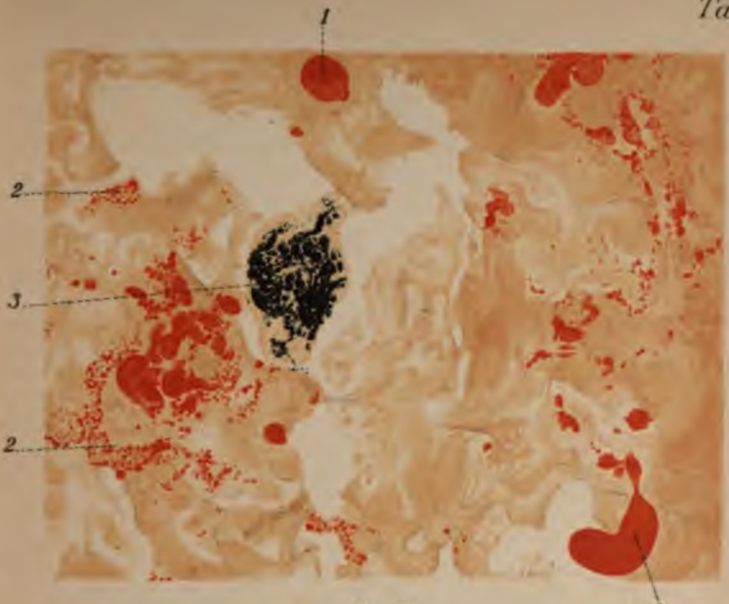


Fig. 1.

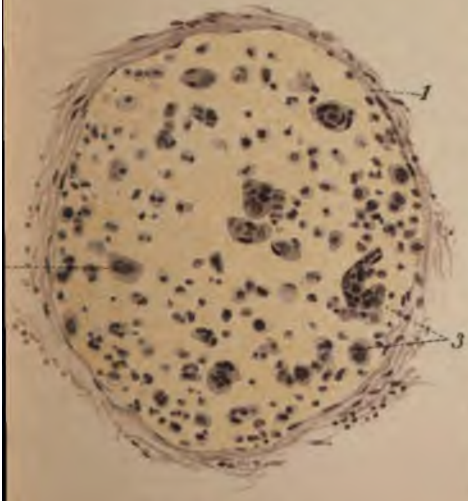
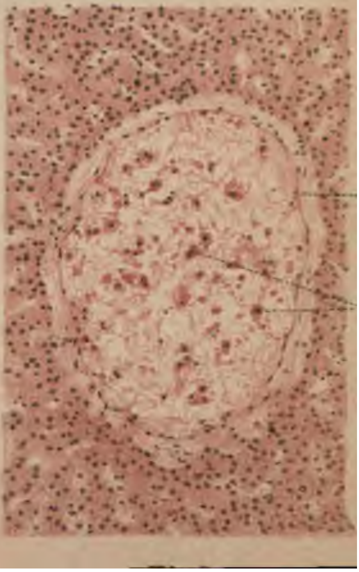


Fig. 2.



placentar, due to the entrance of giant-cells from the placenta into the widely opened uterine veins and their transportation through the right heart into the pulmonary capillaries. The embolus usually consists of multinuclear masses derived from the covering of the villi which project into the intervillous spaces. The accident occurs most frequently in puerperal eclampsia and chorea gravidarum, but is occasionally observed in cases in which labor and puerperium have been normal. These cells also are entirely passive. Whenever active proliferation has been observed after they had been carried into the smaller vessels of the lungs the cell was not a normal placentar cell, but derived from a tumor which had its origin in the placenta—the so-called chorio-epithelioma.

A third variety of embolism consists of *giant-cells from the marrow of bone* [and of other cells in the marrow.—Ed.], which are sometimes washed into the blood-stream and also lodge in the first capillary system that they enter —that is usually pulmonary, as they are much too large to pass through the small vessels. The separation of these giant-cells or of cells containing gigantic nuclei from bone-marrow and their passage through the thin-walled veins of the marrow obviously may take place without difficulty, for the condition often occurs after concussion of bone, after operative procedures, and often in various acute diseases (Aschoff), in erysipelas, pneumonia, typhoid and diphtheria. [Cells from the spleen and the lymph-glands may also form emboli.—Ed.]

Tumor cells of various kinds also may enter the vascular system and thus be carried to points considerably removed from the tumor. This process represents the most important factor in the formation of metastatic tumors. The faculty of entering the blood-vessels varies greatly in different kinds of tumors, and usually goes hand-in-hand with the clinical conception of so-called malignancy. The entrance into the circulation may be effected either by active proliferation through the vessel-walls or by primary softening of certain portions of the tumor and by destruction caused by hemorrhages. The significance of this kind of embolism consists in the fact that in many cases at least, especially in tumors that are clinically known as malignant, the separated tumor cells, after they have been washed into a remote portion of the circulation, retain the power of active and unlimited proliferation of similar tumor cells, and a true implantation of new tumor germs is thus effected, every cell that is carried to a distant portion of the body becoming the mother cell of a new tumor, the so-called *metastatic tumor* (see Plate 7, Fig. 2, and Plate 77, Figs. 1, 2).

In cases of laceration and inflammation of the subcutaneous fatty tissue, especially after severe contusion, after injury of the pelvic cellular tissue, and of the fatty bone-marrow in the diaphysis of the long bones, particles of the disintegrated fat often enter the open venous channels and make their way into the right heart and from there into the pulmonary capillaries. Thus results the so-called *fat-embolism.* Depending on the extent of the destruction of tissue, the pulmonary capillaries in fresh microscopic sections are found to be more or less extensively filled with intensely refractive, branching, sausage-shaped masses, which on teasing sometimes resolve themselves into small, glistening fat-droplets (compare *Atlas of Special Pathologic Histology*, Vol. I., Plate 35).

These masses of fat that have been wedged into the small arteries and capillaries may be demonstrated beautifully by fixing frozen sections in formalin and staining with sudan (Plate 7, Fig. 1). Sometimes an entire alveolus may be surrounded by capillary vessels filled with fat, which look as if they had been injected. Sometimes the occlusion of the pulmonary vessels with fat may be so extensive that the interchange of gases on the respiratory surfaces is diminished to the point of shortening life, and many cases of sudden death after slight injuries, associated with extensive contusion of fatty tissue, may be explained in this way. Fat-embolism, however, does not necessarily imply a severe injury or extensive destruction of tissue. Ribbert has shown that it may be produced experimentally by tapping a rabbit two or three times on the tibia with a wooden instrument, by letting it fall to the ground from the height of a table, or by holding the animal by the ears, and without using much force, letting it swing against a wall. It is true that in these cases the fat-emboli are correspondingly small. The fat may, under certain circumstances, pass through the pulmonary capillaries, enter the left heart, and be carried into the capillary region of the greater circulation, where it generally produces occlusion in the domain of the coronary vessels of the heart, with consecutive degeneration of the myocardium, or lodges in the brain and leads to the production of multiple ecchymoses.

Parasitic organisms, especially bacteria, may enter the circulation in such masses as to occlude a limited vascular region; these are known as *bacterial emboli.* Especially the so-called mycotic, malignant, or ulcerative endocarditis, in which there are extensive deposition and multiplication of pyogenic organisms on the valves of the heart, is a most prolific source for the dissemination of bacteria throughout the entire body, a process which, owing to the pyogenic action of the bacteria wherever they are deposited, leads to multiple embolic abscesses and the clinical picture of septicopyema. Owing to the extremely destructive, toxic effects of the micro-organisms thus diffused over the entire body, death usually occurs early—often so early that accumulations of pus-corpuscles around the bacteria at the time of death have not yet formed. In such instances microscopic examination reveals an uncomplicated picture of bacterial embolism and when, as usually is the case, the bacteria are pyogenic cocci, of coccal embolism (Plate 6, Fig. 1). If the process is not generalized over the entire body at the same time so that only certain capillary regions—as, for instance, that of the heart muscle—are affected, then coccus-embolism is sometimes followed by the formation of *embolic abscesses.* Masses of leukocytes surround the embolus and infiltrate the adjoining tissue. If their growth is active enough, the cocci may penetrate the vessel-walls and escape into the outer tissue; owing to the dense accumulation of pus-corpuscles and the disintegrative action of the pyogenic cocci, partial melting-down of the tissue with the formation of a pus cavity takes place—embolic abscess. After the death of the micro-organisms the embolic abscess may heal if the process is limited. In the heart muscle, especially, where embolic abscesses are quite common in acute endocarditis, they form one of the common sources of cicatrices and indurations of the myocardium, as described at length in Vol. I. A typical occurrence is the accumulation, by a process of filtration, of the micro-organisms circulating in the body in large plugs or sausage-shaped masses in the narrow capillaries of the kidneys and in the glomeruli, where in many cases of pyema the vessels are sometimes absolutely injected, as it were, with micro-organisms. In the liver also, after infection of the navel (purulent omphalitis) in the newborn, as well as in animals, pure coccus-emboli are observed occasionally, as also in destructive mycotic processes in the region of the portal vein. If life is sufficiently prolonged, the emboli in these cases also lead to the formation of abscesses, and if the latter have their origin in embolic thrombi, the condition is described as pylethrombophlebitis. It is almost needless to say that other micro-organisms besides pyogenic cocci, such as tubercle bacilli, the bacillus of anthrax and of the plague, may also lead to the formation of emboli.

Finally, a form of embolism should be mentioned which is due to the invasion of the blood-current by so-called *exogenous pigments* (see under Pigments). In the lungs, especially, a deposition of dust particles in the immediate neighborhood of minute blood-vessels often takes place. These particles may be carried by the migrating cells to the intima of the vessel and even into the lumen, whence they may be carried further along with the blood-current and thus lead to the metastatic deposition of pigment in remote organs, as the spleen and kidneys. In senile individuals these organs sometimes present quite a well-marked anthracosis. This pigment may, however, enter the circulation by other channels, especially by direct rupture of enlarged lymph-glands, overloaded with pigment and the seat of chronic inflammation, a process which is not at all uncommon, especially in case of the peribronchial glands at the hilus of the lungs, and which leads to more or less extensive flooding of the blood-channels with pigment (see Vol. I., Lymph-Glands.)

INFARCT.

It has already been stated that the effect of complete interruption of the blood-supply on the tissue is designated infarction. By this term is understood the visible effect on a definite portion of tissue of cutting off the blood-supply. This is, of course, subject to extraordinary variations, the gravity of the result depending on the individual tissue and the arrangement of the blood-supply of the corresponding organ or section of an organ. If collateral circulation is well developed in a certain organ, the effect of occlusion of a single arterial trunk is readily overcome, as the part which has been cut off at once receives a sufficient nutrient supply from the existing lateral branches of the occluded vessel. As a matter of fact, it is not uncommon at autopsies to find in organs with well-developed collateral branches more or less extensive thrombosis or embolism without any visible effect on the tissue concerned,—as, for example, in the larynx, where even a large arterial trunk may be occluded by an embolus without leading to infarction. In other organs the injurious effect of interrupting the supply of nutrient material by occlusion of an arterial branch at once becomes apparent, the corresponding tissue falling a prey to local death or necrosis. This is peculiarly the case in organs or parts of organs provided with so-called end-arteries, in the sense in which the term was used by Cohnheim—*i.e.*, with arteries which give off no connecting branches or collaterals before they break up into capillaries. When an end-artery becomes occluded, the nutrient supply to the corresponding tissue is completely cut off and the resulting necrosis manifests itself first in an increased consistence, a slight increase of volume, and extraordinary pallor as compared with the surrounding tissue. As the region supplied by an end-artery is usually triangular or pyramidal in shape, the resulting infarct also presents that form, the embolus which occludes the corresponding artery being found at the apex of the pyramid, while the base usually presents toward the surface of the organ. The minute processes that take place in the cells and in the intercellular substance of the infarct will be discussed more in detail in connection with necrosis; for the present it will suffice to mention that the visible alterations depend upon coagulation of the fluid cell-albumin, and that the process is, therefore, designated *coagulation necrosis.*

When formation of infarct after embolism is studied under the microscope,—as, for example, in the frog's tongue after the introduction of small corpuscular elements into the circulation,—the first change noted on the proximal side of the embolus in the afferent artery, as well as on the distal side in the capillaries and the corresponding vein, is *stasis* or arrest of the blood column. As a rule, the artery is collapsed behind the plug and up to the point where it breaks up into capillaries, but beyond that point movement in the blood is seen in the vessels of the infarcted region, but in the opposite direction, fresh blood being poured in centrifugally from the vein; the blood may flow through the entire capillary region as far as the artery, and sometimes as far as the occluding plug. As, however, the embolus is a permanent obstacle to the reëstablishment of the circulation, and as the blood-vessels of the infarct, being already damaged, are unable to offer sufficient resistance to the blood-pressure, extensive *diapedesis of red blood-cells* soon takes place, the elements crowding through the cement substance between the endothelial cells in great numbers (see Diapedesis), and forcing their way into the surrounding tissue, which is already necrotic. This emigration of red blood-cells may be so great that the necrotic tissue eventually becomes packed with them, and the originally colorless or white *anemic infarct* is converted into a dark-red, *hemorrhagic infarct.* But this backward flow of blood from the vein does not necessarily occur in every case. The infarct may remain permanently anemic, and, therefore, pale in color, or the hemorrhage by diapedesis may be limited to the peripheral vessels of the infarct, and there results an anemic infarct with a hemorrhagic marginal zone—the commonest effect of occlusion of an end-artery. It is possible, also, for parts of organs which are supplied with a well-developed collateral circulation to undergo infarction, especially in the case of circulatory abnormality. In such cases, however, there is always a subsequent reëstablishment of circulation in the infarcted area, and if this occurs early enough, the tissue may escape necrosis. But if damage to the vessel-wall within the affected tissue has already taken place, then the vessels may be unable to resist the pressure, just as in the case of backward flow from veins; the constituents of the blood pass through between the gaping endothelial cells as through a sieve, and enter the tissue, again resulting in the formation of a hemorrhagic infarct. It follows, therefore, from what has been said, that the presence of a hemorrhagic infarct does not necessarily imply the existence of collaterals in the corresponding region.

Within the infarct the blood which is stagnating in the vessels, as well as that which has extravasated more or less densely into the necrotic tissue, undergoes coagulation. If the coagulation is confined mostly to the vessels, extensive, delicate, and reticular fibrin thrombi are sometimes formed, so that with a suitable stain the tissue appears as though injected. The entire infarct, whether it be hemorrhagic or not, being dead tissue, acts like a foreign body and dissolves particles of tissue carried into the surrounding regions by the plasma, and produces inflammatory changes. The effect of this inflammatory irritation soon appears in the formation of a thick wall of leukocytes with fragmented nuclei, which surround the necrotic focus on all sides and even penetrate to a certain depth. This infiltration with leukocytes, however, is only a temporary phenomenon; the white blood-cells themselves have no special import on the subsequent processes; above all, because they are not capable of forming new tissue and are only the precursors of a new cell-formation, which grows into the infarct uniformly from all directions in the shape of a coherent, embryonal, extremely vascular connective tissue, the so-called granulation tissue, which gradually penetrates every portion of the infarct, and ultimately displaces it as fast as the necrotic material undergoes solution and absorption.

Here, as everywhere else in the body, the removal of necrotic masses after local death does not result in a gap, —the so-called reparative tissue,—which, although it is not equivalent in functional power to the original tissue of the organ, at least, so far as the volume is concerned, compensates for the loss. In the same way as has been described in connection with the organization of thrombi the surrounding tissue sends sprouting buds of young, spindle-shaped, and polygonal connective-tissue cells, rich in protoplasm (fibroblasts), and of spheric, migratory cells with darker nuclei, into the spaces left by the absorption of the necrotic tissue; the vessels put out pointed, and at first solid, branching, endothelial plugs, which, as the cells gradually separate, become filled with blood; ultimately the entire infarct is penetrated with this granulation tissue. The active cell multiplication is readily recognized by the abundance of mitotic figures in the endothelium and in the young connective-tissue cells. This newly formed tissue is extremely rich in cells and succulent, from the abundance of protoplasm in the individual elements; it is soft, and traversed by numerous, thin-walled vessels distended with blood; it not only fills the gap, but during its early stages even projects beyond the level of the surrounding tissue. When a hemorrhagic infarct undergoes organization, the extravasated red blood-cells, of course, undergo all the processes that ultimately lead to pigmentary metamorphosis and which have been described in the section on Hemorrhage. For some time after the formation of the infarct pigment fragments of a brownish color may be seen, both in the invading granulation tissue and in the surrounding tissues, partly within the cells and partly free. Sometimes the boundary zone is occupied by a dense ring of blood-pigment. But this young, succulent granulation tissue also merely represents a temporary stage; as a result of the formation of fibrils, contraction of the protoplasmic fibroblasts and their nuclei into delicate, spindle-shaped cells, and obliteration of the numerous wide blood-vessels, it gradually changes more and more into a dense fibrous connective tissue containing but few cells, which ultimately assumes the character of cicatricial tissue, and, owing to increasing contraction, it is gradually depressed more and more below the level of the surrounding tissue, so that ultimately nothing but a retracted, funnel-shaped scar, with a thin fibrous layer, betrays the site of the original infarct. As in the case of thrombi, a secondary deposition of lime salts may take place in the cicatricial tissue, converting it into an extremely hard mass.

If the embolus which caused the infarct contained micro-organisms, the purely physical effect is from the beginning associated with the specific activity of the micro-organisms in question; the leukocytes in such a case often accumulate in such numbers that the tissue melts down, thus forming an embolic abscess, which has been fully described in the foregoing. Such embolic abscesses, as has been remarked, are also capable of healing under certain conditions—*i. e.*, regenerative processes take place and ultimately result in the formation of a scar.

Infarcts in the central nervous system occupy a special position. Instead of undergoing firm coagulation, which cannot take place on account of the peculiar chemic composition of nerve substance, the tissue rapidly melts down (colliquation). The necrotic tissue is converted into a semifluid mass consisting of myelin and fat-droplets, and the region supplied by the obstructed vessel is occupied by a focus of softening (encephalomalacia). The myelin and fat-droplets are rapidly taken up by migrating, contractile cells, which may be completely loaded with droplets, being then known as "granule cells." These cells effect absorption of the necrotic material in that they wander back into the lymph-channels and convey the masses of detritus to the lymph-stream, in which they are carried off. After a time the softened mass of nerve substance may be partially or even totally removed, and at the same time granulation tissue grows in from the surrounding tissue, as in the case of a solid infarct. The granulation tissue either occupies the entire focus of softening and results in a solid scar, or a connective-tissue capsule gradually grows around the focus and the remains of softened tissue within this capsule, becoming mixed with fat and granule cells, take on a milky appearance, or a turbid brownish fluid results from the admixture of blood. This structure is known as a cyst.

II. ATROPHY.

THE term atrophy is applied to the diminution in the volume of an organ without disturbance of its chemic composition and structure, the latter, at least, being in the main preserved. Atrophy, therefore, distinctly differs from degenerative processes, which are always accompanied by profound changes in the physical and chemic composition of tissue. Atrophy may consist either of a reduction in the size of the elements of the organ or in a reduction of their number. The latter variety is also designated *numeric atrophy*.

A distinction is often made between *active* atrophy, which is due to inability on the part of the cells to assimilate the nutrient material, and *passive* atrophy, in which the disappearance of the tissue is due to a deficiency in the amount of nutrient material supplied to the cells. In many cases a combination of the two processes is at work, and it is often impossible to determine from the final product in what manner the atrophy has taken place.

Many tissues of the body are constantly used up in the vital processes. Some material is used up, either by being rubbed off or disseminated, as on the skin and many mucous membranes, or the protoplasm of the cells breaks down and is utilized for the formation of special secretions. In all these cases the cells are replaced by a process of physiologic regeneration of the cellular constituents that have been used up. It is needless to say, however, that the power of regeneration and proliferation of new cells capable of function is not unlimited; a stage may be reached in which regeneration is defective and ultimately ceases entirely, either in individual organs or in the entire body. This condition is also physiologic and is undoubtedly connected with the senile phenomena in the body. It is also obvious that the inability to produce new cells in the individual organs is not lost suddenly, nor is such loss at once followed by a loss of function in the cor-

PLATE 8.

Fig. 1.—**Extreme Atrophy of Liver-cells in Congestion of the Liver** (Stained after Romanowsky with methylene-blue, eosin. × 66.): 1, Central vein; 2, intact liver tissue in the peripheral parts of the acini; 3, greatly dilated capillaries of the portal vein; 4, isolated remains of liver-cell cords between the capillaries.

Fig. 2.—**Atrophy from Disuse of a Muscle in an Amputation Stump of the Thigh** (Hemat. × 280.): 1, Approximately normal muscle fibers, showing increase in the nuclei of the sarcolema; 2, greatly attenuated muscle-fibers; 3, spindle-shaped attenuated muscle-fibers; 4, fibrous tissue.

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responding organs; it betrays itself rather in a gradual reduction of vital phenomena, frequently associated with shrinking of the corresponding parts of the body, and this process, to which nearly all the tissues of the body may be subject, is known as *senile atrophy*. As it always occurs in advanced age, and is, therefore, physiologic, it does not, strictly speaking, belong to the domain of pathologic processes; but under certain circumstances it may make its appearance prematurely in individual organs or in the entire body. Under the influence of morbid changes in special organs it may occur in other organs or parts of organs, and for these reasons it may possess a decided pathologic importance. Senile atrophy in part depends on actual physical wearing-out of the corresponding tissue elements; thus, for example, the elastic fibers in the skin, the lungs, and the vessels in course of time become worn out and flabby from the loss of elasticity, in the same way as a worn-out rubber band.

In part senile changes also depend on defective nutrition of the tissue, owing to changes in the blood-vessels which occur almost regularly with advanced age, and these changes again are based on the physiologic wearing-out just mentioned.

Deficient nutrition is also followed by insufficient regeneration of cells and disappearance of the substances which subserve the nutrition of the cells.

Thus, for example, senile atrophy manifests itself in the skin by a thinning of the epidermis, the layers of the

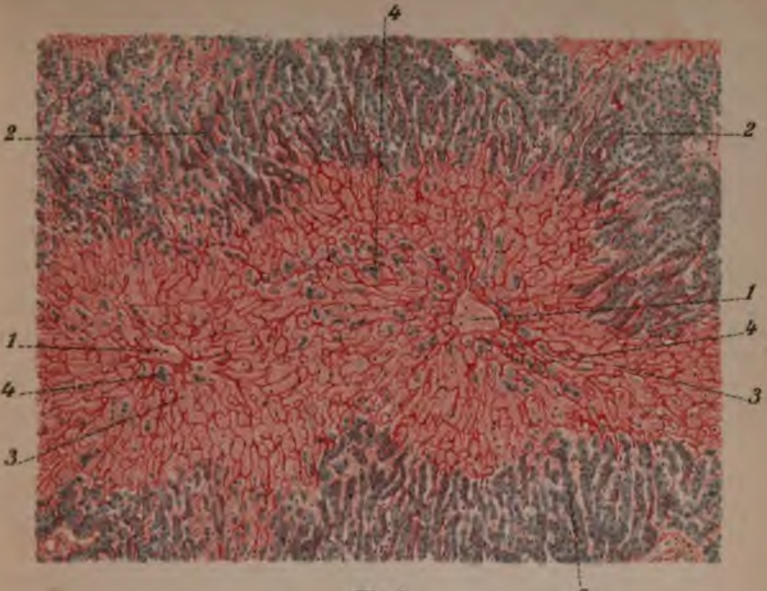
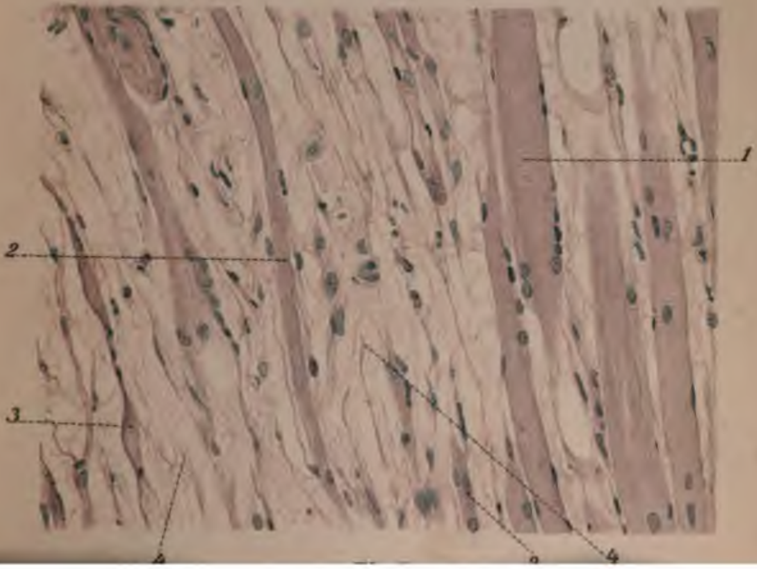


Fig. 1.



stratum mucosum especially being diminished in number; the cells appear smaller, the papillary body is low and flattened, the corium in many places is thin, and its elastic elements have disappeared, the individual elastic fibers being sometimes broken up into short pieces.

Senile atrophy shows itself conspicuously in many glands. In the sexual glands physiologic atrophy takes place normally after the cessation of the regular sexual function. In the ovaries the Graafian follicles contract, ovulation ceases, the tunica albuginea becomes thick, and forms a dense, tough envelop of connective tissue, which surrounds the entire organ. From the latter, as well as from the corpora fibrosa and the interstitial tissue, an active new formation of connective tissue takes place which is followed by progressive cicatricial contraction, so that the entire organ ultimately is converted into a small hard body, consisting chiefly of connective tissue. In the male sexual glands the connective-tissue formation is not so prominent a feature of senile atrophy. Spermatogenesis ceases, the epithelium of the seminal ducts is lower than normal, and in many cases a deposition of an abundant brownish pigment is seen. The surrounding connective tissue is increased, and there are often found larger or smaller groups of epithelioid cells—the so-called "interstitial cells" (Zwischenzellen) (see *Special Pathologic Histology*, Vol. II.). With advancing age the lymphatic apparatus and the spleen shrink in volume, with decrease in the cellular constituents, because the regeneration of blood and lymph is diminished and the demand on the activity of these organs accordingly is much lessened (see Atrophy from Disuse). Here also, especially in the spleen, an abundant deposition of pigment takes place in the form of large accumulations of brownish fragments scattered through the tissue, and this probably bears some relation to the increased destruction of red blood-cells.

The heart, the liver, the kidneys, and the central nervous system also undergo senile atrophy in advanced age, and a similar process takes place as the result of a general cachectic condition. In the heart the individual muscle fibers become attenuated; the fibers sometimes appear to be only half as broad as in the normal organ; the transverse striation is preserved in the superficial portion, while the central portion of the cells, on the other hand, is obliterated by the deposition of large spindle-shaped masses of fine, granular, brownish-yellow pigment (*brown atrophy of the heart muscle*). The origin of this pigment, which is seen in so many atrophic organs, has not yet been satisfactorily explained. In part it appears to be due to an increased disintegration of red blood-cells; in part also to metabolic activity of the cell protoplasm itself (see under Pigment). In the heart the process is often associated with swelling and loosening of the cement substance [which becomes visible.—Ed.], causing increased friability of the muscle. The liver presents a diminution in the size of the acini, caused chiefly by disappearance of the cell trabeculæ in the central portions, accompanied with deposition of brownish pigment-granules. In a transverse section of a certain size more acini are found than would occupy the same space in a normal section. The liver-cells nearest the central veins are diminished in all their diameters.

In the central nervous system the atrophy is found, on microscopic examination, to be most marked in the neurocytes, which are diminished in all their diameters and often reduced to narrow, spindle-shaped corpuscles; Nissl's granulations are diminished; and brownish, or even brownish-black, pigment is often found. In the fatty tissue and in the bones senile atrophy reveals itself in very definite histologic processes. In adipose tissue (see Fig. II.) the individual fat-cells are greatly reduced in size and loosened in cohesion. The fat-cell, instead of being a spheric structure with a large fat-drop occupying almost the entire cell with but a narrow protoplasmic body and a crescentic nucleus, is converted into a polygonal, and in advanced cases spindle-shaped, structure, containing in its protoplasm several fat-droplets of various sizes, which, taken altogether, fall very much short of the normal. Individual cells may be entirely free from fat and appear rather as narrow spindle-cells. The fibrous substance under such circumstances becomes very distinct, and the gaps formed by the disappearance of the fat-cells are often filled in with a watery or thin mucoid fluid, giving the fat tissue a flabby, gelatinous appearance. In the contracted fat-cells, as well as in the connective tissue, brownish granules of pigment frequently occur, and in the connective tissue, owing to the disintegration of individual cells, there may be small, free fat-droplets. The best specimens of this atrophy of fatty tissue are found in the subpericardial fat in old persons or cachectic individuals, with simultaneous and advanced atrophy of the heart.

In advanced age the skeletal system usually undergoes marked atrophy; certain portions of bones disappear altogether and are disposed of by the activity of absorbing cells, as, for example, the alveolar processes in the aged after loss of the teeth. The long bones also, as well as the spongy and flat bones, suffer a diminution of their substance, and the loss in volume and weight in these parts is often astonishing. In the long bones, for example, the compact cortical layer becomes progressively thinner, the inner surface is covered by large multinuclear cells derived from the marrow (osteoclasts), and the bone-substance in these places is eroded, leading to the formation of pit-like depressions (Howship's lacunæ) which later coalesce and thus lead to progressive thinning of the bony lamellæ. The medullary spaces consequently increase in size (eccentric atrophy). Disappearance of the trabeculæ of the spongy bone-substance also takes place from the activity of osteoclasts and the formation of lacunæ. This process may reach such a point in the ribs, for instance, that the cortical layer is reduced to a fine lamella not much thicker than paper and very brittle, and the trabeculæ in the spongy substance of the dilated medullary cavity are converted into delicate, widely separated ridges (Plate 9, Fig. 1).

Atrophy of a tissue is often caused by long-continued pressure, a condition which is designated *pressure atrophy.* In this form also complicated melting-down processes—

PLATE 9.

Fig. 1.—**Senile Atrophy of a Rib** (Alum-cochineal; Bleu de Lyon. × 40): 1, Greatly narrowed cortical lamella; 2, rarefied trabeculæ in the spongy substance; 3, periosteum; 4, holes in the marrow-fat; 5, accumulations of marrow-cells.

Fig. 2.—**Atrophy of Uriniferous Tubules in the Kidneys in Arteriosclerosis** (× 170): 1, Uriniferous tubules of normal width; 2, increased interstitial connective tissue, with round-cell infiltration; 3, compressed, extremely atrophic uriniferous tubules; 4, glomeruli, for the most part obliterated and converted into connective tissue.

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as, for instance, in bone—often take place; or the atrophy merely represents a diminution in the volume and a contraction of the individual elements. The essential parenchymatous portions usually arrange themselves in a layer lying parallel to the surface of the compressing body—as, for example, when an echinococcus cyst develops in the liver and causes atrophy in the surrounding liver tissue, and in the constriction, caused by tight lacing, which is most marked in the right lobe of the liver [“liver of lacing.”—Ed.]. In chronic passive congestion abnormally distended blood-vessels may cause compression of parenchymatous portions, and if the compression lasts long enough, the organ may undergo general atrophy. This is seen, for instance, regularly in chronic congestion of the liver (Plate 8, Fig. 1), in which the central portions of the acini are abnormally distended for a considerable period of time by the overloading of the central veins and the contiguous portions of the capillaries of the portal veins. The dilated blood-vessels compress the cords of liver-cells lying between them, the latter become narrower and narrower, and ultimately suffer a solution of continuity or even complete dissolution, so that on histologic examination the central acini appear to consist of cavernous blood-spaces, in which are seen at most only a few scattered liver-cells.

Shrinking of the essential constituents of organs from round-cell accumulation in chronic inflammatory conditions also furnishes a good example of pressure atrophy—

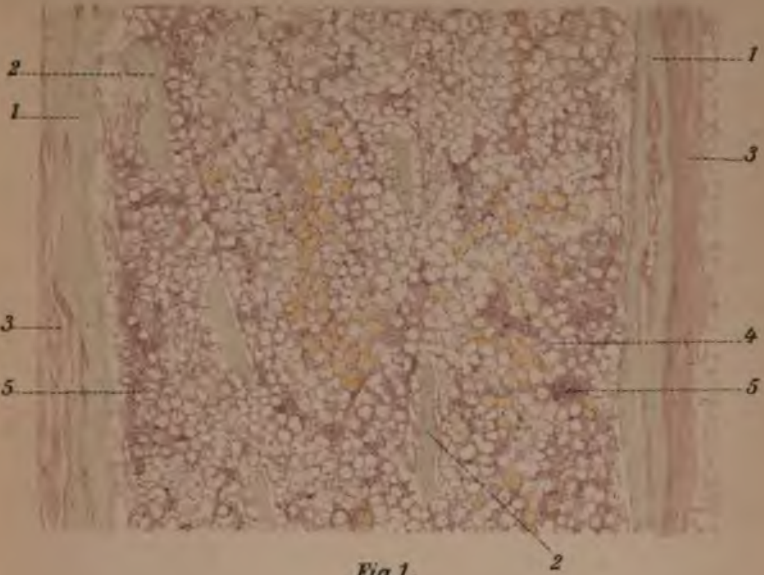
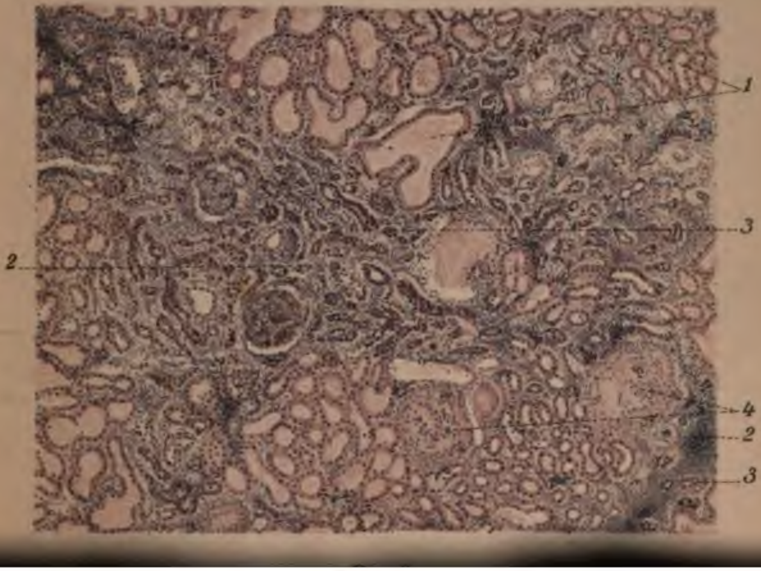


Fig. 1.



e. g., the atrophy of uriniferous tubules and sometimes of glomeruli in chronic inflammation of the interstitial tissue with the production of large deposits of cellular and fibrous connective tissue (Plate 9, Fig. 2).

It is well known that when an organ has ceased to perform its physiologic function for any length of time it undergoes atrophy; this form is known as *atrophy from inactivity*. In the last instance it is probably also due in part to defective nutrition. Thus, for example, if muscular exercise is persistently neglected, the blood-supply to the muscles diminishes. In a similar manner glands whose function has been abolished are likely to undergo atrophy. Atrophy from inactivity is readily demonstrated, for example, in muscles after amputation, for the distal point of insertion is absent and regular contractions are impossible; or in muscles the connection of which with the central nervous system has been destroyed by a loss of continuity in the motor nerves. Such muscles soon begin to show progressive atrophy, the individual fibers become more and more attenuated, although transverse striation may be preserved for some time, even when the fibers have become reduced to extremely narrow strips or to mere shreds with spindle-shaped enlargements at regular intervals (Plate 8, Fig. 2). The atrophy is accompanied frequently by an increase in the nuclei of the sarcolemma. Ultimately the contractile substance disappears altogether and the remaining fibers cannot be distinguished from the interstitial tissue. The atrophy does not progress uniformly, but rather in patches, fibers with transverse striations being preserved for some time at individual places, while in other places nothing but longitudinally arranged fibrillar tissue remains.

It is needless to say that diminution in the nutrition of a tissue, an organ, or of the entire body is followed by atrophy of the corresponding mass tissue—*atrophy from disturbed nutrition*. It is well known that during starvation the individual cells of many organs suffer a considerable diminution in size. Manassein, for example, demonstrated that the diameter of the liver-cell in rabbits, which normally measures on the average 22.3 μ, may be diminished to 8.9 μ during starvation. In the muscles also simple atrophy from starvation may attain a considerable degree. Owing to the contraction of the arteries in arteriosclerosis and atheroma, many organs, as, for example, the kidneys, may suffer great diminution in size, the atrophy being, as a rule, not uniformly distributed over the organ, but affecting individual portions more severely than others, so that granulation [and often great irregularities.—Ed.] of the surface results (arteriosclerotic atrophy of the kidneys).

Finally, certain other forms of atrophy are observed when the connection between the corresponding organ and the central nervous system has been severed, or in the presence of degenerative conditions in the nerve-center itself (*neuropathic atrophy*). This form of atrophy is attributed to abolition of the nervous influences which control the nutrition of the tissues, and in this sense neuropathic atrophy also belongs to the category of atrophy from disturbed nutrition.

III. RETPOGRESSIVE METAMORPHOSES.

DEGENERATIONS.

I. Cloudy Swelling.

Cloudy swelling, albuminous degeneration, or granular degeneration represents the mildest degree of the degenerative processes in the body, because it is evident that in many cases it may subside and the affected organ may undergo a complete *restitutio ad integrum*. Cloudy swelling most frequently attacks the large, parenchymatous organs, especially the kidneys, the liver, and the striated muscles, and among these especially the heart muscle. Even to the naked eye the changes in the organs are quite apparent; the volume is increased; the consistence is diminished; the tissue is friable and soft; on cut sections the parenchyma bulges; the transparency of the tissue is considerably diminished, so that the light cannot, as under normal conditions, penetrate to a certain depth of the parenchyma. The color of the latter is a uniform opaque gray; the quantity of blood contained in the organ is usually diminished; and an abundance of opaque, finely granular parenchyma juice can be scraped from the cut surface. In severer grades of the condition the affected organs on transverse section present the appearance of having been boiled, and microscopically it is found that the structure of the tissue is considerably distorted. The nature of the process is best studied in recent unstained preparations. As a rule, small particles removed with the scissors can readily be teased out in a drop of saline solution and separated into their component parts. The parenchymatous cells are found to be almost uniformly enlarged. In the kidneys, for example, the transverse diameter of the uriniferous tubules is increased; in transverse sections the lumen is practically occluded by the swollen, blunt epithelial cells that have been forced into the lumen like wedges. The outline of the cells, as a rule, are fairly well preserved, and sometimes the delimitation is even sharper than under normal conditions, evidently on account of the loosening of the cement substance. The cell nuclei are almost everywhere obscured; at best they may be indistinctly seen here and there as vague, shadowy structures. The cell-bodies are filled with a uniform, very fine, dust-like, opaque substance, the individual particles of which are immeasurably small; sometimes slightly refractive, opaque, gold-gray granules stand out more clearly among the particles of the cloudy material, and some larger, spheric, sharply outlined, glistening spheres may be seen. When this deposit is tested with various chemic reagents, the following microchemic reactions are obtained: The granules dissolve in dilute alkalis, as, for example, in a 1 per cent. solution of caustic potassium or sodium; the cell-bodies throughout their extent clear up, and the nuclei suddenly reveal themselves distinctly as the protoplasmic body becomes transparent, although, of course, there is no change in the volume of the cells. When a teased preparation of this kind is treated with dilute acetic acid, the granules at first become uniformly swollen; but as more of the reagent is added they become dissolved in the excess of the acid, and, as with alkaline solution, the cell clears up completely and the nuclei become visible. The addition of a sugar solution followed by sulphuric acid gives the granules a reddish color; iodin (as in Lugol's solution) colors them brown. They also yield the xanthoprotein reaction—*i. e.*, on the addition of nitric acid the granules are stained an intense yellow, showing that the dust-like opacity consists of very minute granules of albumin. The cloudy swelling accordingly consists in an extensive accumulation of undissolved granular albumin in the parenchyma cells.

The liver-cells present similar appearances when affected by cloudy swelling. In this case a study of a thin frozen section is most instructive, as it shows at the same time *both the great* swelling and the uniform, dust-like clouding of all the cells, as well as the marked change in their outlines. The cells are no longer of a regular cuboidal shape, and the impressions made by the capillaries have disappeared altogether; the walls bulge in all directions, the cells being more spheric in shape. At the same time the connection between the individual cells becomes much less intimate because the contact surfaces of the individual cells are greatly diminished. The trabeculæ, instead of being formed of continuous rows of cells, present many interruptions and kinks; the entire cell material looks as if it had been shaken up in an irregular fashion, and its physiologic coherence destroyed, a condition described by Browicz as *dissociation* of the liver-cells. The nuclei, as a rule, are no longer visible, just as in the case of the kidney, but are merely indicated here and there as shadows. Scattered among the dust-like, minute granules a few strongly refractive, spheric masses are almost always observed. When the acetic acid or alkali test is applied, the granules are converted into soluble acid or alkaline albuminates, while the glistening spheres are not affected.

In the *heart* the process leads to swelling of the muscle-cells, chiefly in their transverse diameter; the transverse striation is generally preserved, but is less distinct than in the normal muscle; the double refractive substance appears particularly opaque, and the entire cell, as in the case of the liver and kidney, is filled with innumerable minute granules which cover up the nuclei and give the above-described reactions. As a rule, the cement ridges around the muscle-cells are enlarged, or the individual cells actually appear loosened from their connections and sometimes present transverse fissures, so that they present, in addition, the picture of so-called *fragmentatio* [segmentatio.—Ed.] *myocardii*, which, however, is to be attributed to agonal or postmortem changes. In fact it is always necessary, in examining striated muscles, to guard against mistaking postmortem appearances for cloudy swelling, for the occurrence of rigor mortis is accompanied by a uniform opacity, with the deposition of spheric granules in the muscle-cells which are distinguished from

PLATE 10.

FIG. 1.—**Cloudy Swelling of the Liver in Scarlet Fever** (Recent frozen section. × 300.): 1, Enlarged rounded liver-cells filled with dust-like granules; 2, remains of nuclei; 3, individual fat-droplets.

FIG. 2.—**Cloudy Swelling of the Kidneys in Scarlet Fever** (Uriniferous tubules isolated from fresh tissues. × 300.): 1, Epithelial cells from the uriniferous tubules, in which neither the outline nor the nuclei can be recognized, and densely packed with fine, dust-like granules; 2, remains of nuclei recognizable with difficulty; 3, fat-droplets.

FIG. 3.—**Cloudy Swelling of the Liver in Sepsis** (Hemat.-eosin. × 280.): 1, Central vein; 2, swollen, rounded liver-cells that have been loosened from their trabecular arrangement; 3, anuclear cell fragments; 4, bile-pigment.

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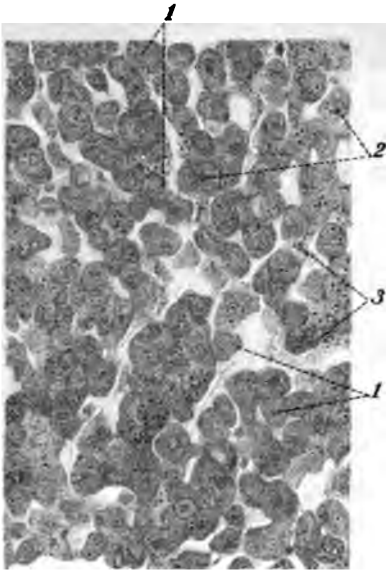
the granules of cloudy swelling by the fact that they are usually somewhat larger and fail to give the reactions mentioned in the foregoing.

In stained sections that have been subjected to alcohol and other preserving fluids the appearance of albuminous degeneration is less distinctly seen. The cloud-like opacity has usually disappeared almost completely, and the nuclei are almost everywhere readily discernible and take the stain. The swelling of the cells, however, and the loosening of their connections can, of course, be recognized; particularly in the liver, the rounding of the cells, and the fact that they are separated from their trabecular connections may be seen distinctly (Plate 10, Fig. 3). Liver-cells with more than one nucleus are not infrequently encountered.

Cloudy swelling is observed principally in a number of severe infectious diseases attended by constitutional symptoms, especially sepsis, typhoid fever, small-pox, scarlet fever, erysipelas, diphtheria, plague, etc. It is also found in certain forms of poisoning, especially acute phosphorus and arsenic poisoning and poisoning with the mineral acids and carbon monoxid. It has also been observed in cases of extensive burns of the skin and after

Tab.1



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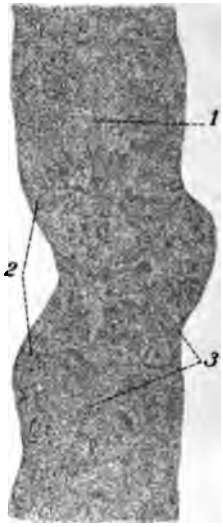
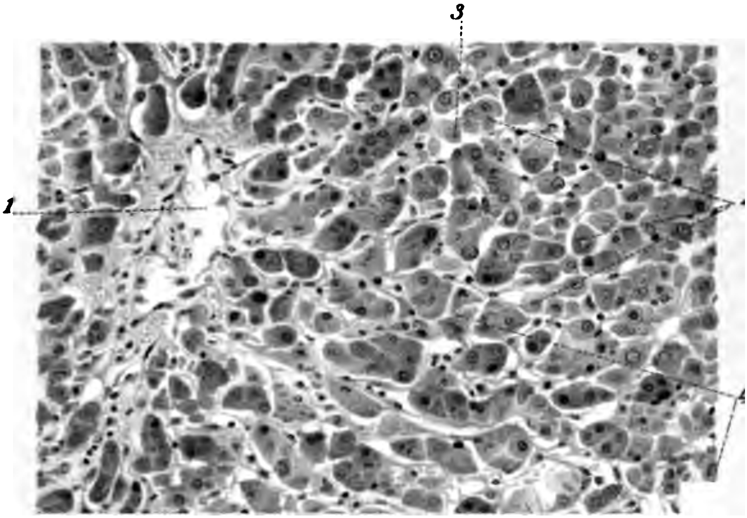


Fig.2.



death from heat-stroke. It is evident that in the infectious diseases just mentioned the bacteria themselves as well as the injurious action of their poisonous metabolic products must be held responsible for the change.

The mode of origin of cloudy swelling is not perfectly understood. Virchow regards it as the expression of a severe nutritive irritation—*i. e.*, the result of increased ingestion of nutritive material under the influence of a definite irritant. He regards it principally as a parenchymatous inflammatory process. According to the opinion of other investigators, the deposition of albuminous granules is due to the accumulation of undissolved, unprecipitated albuminates within the protoplasm, on account of the inability of the cell to assimilate these nutritive materials. It is either the result of an increased supply of nutritive material or of interference with or suspension of the removal of metabolic products.

By means of special preserving and staining methods Altmann has shown that it is possible, even under normal conditions, to demonstrate in the cells of large parenchymatous organs, especially the epithelial cells of the liver and kidneys, fine granules arranged in definite rows around the nuclei (Altmann's granules or bioblasts). It is not clear whether this granulation is an artefact or a natural grouping of preëxisting elementary particles of the cells. But even if they merely represent an artefact, a view which is supported by a number of observations, the fact is, nevertheless, interesting and important, because the granules always present the same appearance in a normal cell when it is treated in the same way. Under pathologic conditions they disappear; nor are they identical with the albuminous granules which occur in cloudy swelling. For, when this condition is produced experimentally in the kidney, as by ligation of the renal vein of the opposite kidney, then Altmann's granules, instead of being increased, diminish in number and disappear altogether after intense albuminous clouding has developed.

Other changes are sometimes observed in the nuclei of tissues the seat of cloudy swelling, especially swelling of

PLATE 11.

Fig. 1.—**Fatty Infiltration of the Liver in Carcinomatous Cachexia** (Frozen section. Sudan stain. × 280.): 1, Central vein of an acinus; 2, liver-cells completely filled with fat-droplets; 3, very minute fat-droplets.

Fig. 2.—**Fatty Degeneration of the Myocardium in Pernicious Anemia** (Frozen section. Sudan stain. × 280.): 1, Muscle-fibers with transverse striation preserved; 2, muscle-fibers in which the striation is completely obscured by the accumulation of fat-droplets; 3, large, free fat-drops.

Fig. 3.—**Beginning Fatty Degeneration of the Kidney in Scarlet Fever** (Frozen section. Sudan stain. × 280.): 1, Extremely small fat-droplets, deposited in the peripheral portions of the epithelial cells of the uriniferous tubules; 2, uriniferous tubules, the epithelial cells of which are in a state of marked fatty degeneration and in part lie free in the lumen.

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the nucleus with enlargement of the surface and diminution of the chromatin framework.

In many cases cloudy swelling, instead of being a simple and isolated process, is accompanied in the same organ by more or less pronounced fatty degeneration, and it is to be supposed that transitional stages between the two conditions also exist.

Fatty Infiltration and Fatty Degeneration (Fatty Metamorphosis).

Even under normal conditions the quantity of fat in the body and in individual tissues is subject to wide variations. The quantity of fatty tissue varies in the same individual at different periods of life. During the earliest years of infancy and in old age the body, as a rule, contains more fat than during middle life. An increased ingestion of fat with the food or the conversion of carbohydrates or even of albumin (Voit, Cremer) may cause an increased accumulation of fat within the body. The stored-up fat is deposited principally in the connective tissue, especially in the subcutaneous connective tissue, *the omentum*, the mesentery, the peritoneum, and in the

Tab. 11.

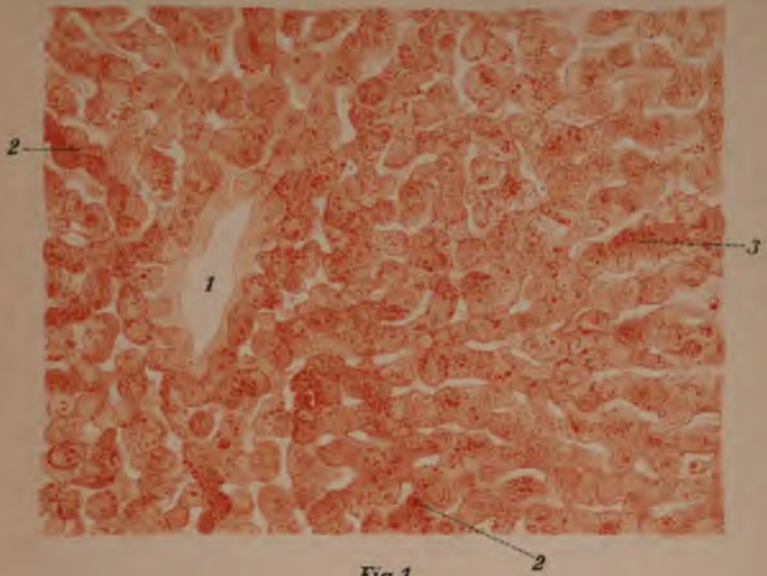
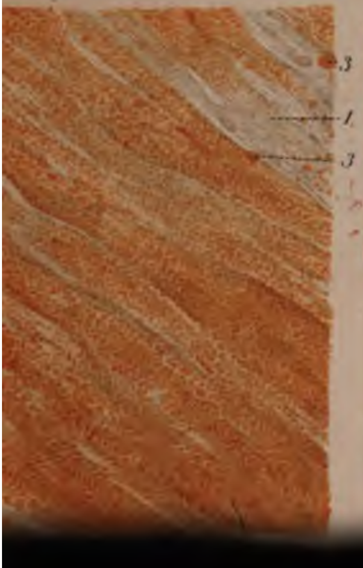
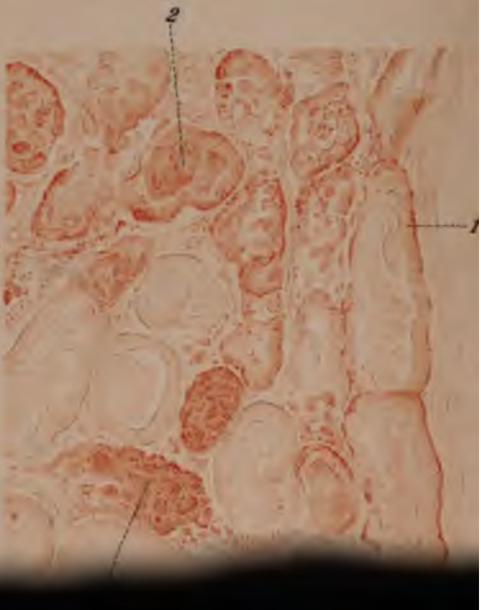


Fig. 1.





mediastinal connective tissue, the epicardium, etc. It is very difficult to say when this fatty infiltration is to be regarded as a pathologic process. The dividing-line between physiologic and pathologic adiposity, obesity, or lipomatosis cannot be sharply drawn.

The mechanism of fatty infiltration consists in the accumulation of fat-droplets which coalesce to form large drops in the connective-tissue cells, which are thus converted into fat-cells. In other words, the process is just the reverse of what takes place in atrophy of fatty tissue, in that the reversion of fatty cells into connective-tissue cells is also accompanied by the appearance of minute fat-droplets. Sometimes the infiltration of connective tissue with fat assumes a distinctly pathologic character by encroaching upon neighboring tissue.

This is seen especially in the heart in *adipositas cordis*, in which a progressive overloading of the intramuscular connective tissue with fat from the subepicardial adipose layer takes place, and complete conversion into fatty tissue gradually follows, the fat penetrating the muscle-bundles and, if the process is severe, bringing on pressure atrophy and extending as far as the endocardium. In universal lipomatosis fat may be stored up even in the endocardial connective tissue and a thin, superficial accumulation of adipose tissue may be found on the inner aspect of the ventricle, separated from the cavity only by a thin layer of connective tissue and the epithelium, and not always continuous with the subepicardial fat.

A similar condition is sometimes observed in the connective tissue of striated muscles, the connective-tissue cells between the muscle-bundles being loaded with fat and converted into fatty tissue, thus forcing the muscle-fibers apart and increasing the transverse section of the muscle, while the muscle-substance itself is diminished (*lipomatosis musculorum; pseudohypertrophy*).

Next to the connective tissue the liver is one of the seats of predilection for the deposition of fat. Under normal conditions, in individuals who are not excessively fat, the cells of this organ always contain a variable quantity of fat-droplets. But the latter may undergo considerable increase both in size and distribution, especially in the peripheral zones of the acini. The fat-droplets in the liver-cells swell more and more, crowd the protoplasm to one side, force the nuclei against the wall so that they become very thin and crescentic, and in severe grades of the process may effect such a diminution of the cell-protoplasm that the peripheral zones of the acini appear to be formed entirely of fatty tissue and completely lose their specific epithelial character. The fat nearly always deposits itself in the form of one large drop in each cell—that is to say, in the same way as in the case of the connective-tissue cell that becomes converted into a fat-cell. This condition is designated *lipomatosis* or *steatosis hepatis* [fatty infiltration of the liver.—Ed.]. It is encountered in general obesity, but especially in chronic diseases which lead to wasting and cachexia, particularly chronic pulmonary tuberculosis and the cachexia due to malignant tumors. The fat with which the liver is infiltrated is in these cases derived from the body-fat, especially from the subcutaneous connective tissue, which is melted down under the wasting influence of the disease, but not completely burnt up and therefore deposited in the liver. This mechanism can be demonstrated experimentally by first starving animals, then feeding them with large quantities of a given kind of fat that is readily identified, such as mutton fat (Rosenfeld), and subjecting them to some influence which is known to produce an increase of fat in the liver, as for example, phosphorus-poisoning. The greater part of the ingested fat in these experiments may be recovered from the liver.

In other organs also a fatty infiltration which falls within physiologic limits is occasionally observed, as, for example, in the kidney, where the peripheral portions of the epithelial cells of the convoluted tubules very often contain minute fat-droplets; in cats and dogs these fat-droplets are regularly found. In diabetes mellitus an increase of this fatty infiltration is observed in the kidneys, although no other pathologic changes can be distinguished in the organs (von Hansemann). In the testicles, not only in old persons and in a senile involution of the body, but also during the middle period of life, collections of minute fat-droplets are sometimes encountered in the epithelial cells of the seminiferous tubules.

For a long time it has been customary to attempt a strict distinction between *fatty infiltration—i. e.*, the deposition in tissue-cells of fat obtained from without—and *fatty degeneration* of tissue-cells, in which the fat is supposed to be produced *in loco* by conversion of the cell-albumin, or protein substances of the cell-bodies, into fat-droplets. Morphologically, the point of distinction between the two processes, which were regarded as genetically distinct, was stated to be that in fatty infiltration the fat is deposited in the form of large, spheric drops, while in degeneration the fat appears in the form of individual little spheres separated from one another by protoplasmic septa. But this distinction cannot be strictly carried out nor is it well founded [as the so-called retrogressive changes are becoming better understood the hard-and-fast distinction formerly drawn between degeneration and infiltration is gradually breaking down.—Ed.]; for it has already been shown that very small fat-droplets may occur in the cells in fatty infiltration, both in the initial stages and when the infiltrated fat begins to break down, as well as in atrophic conditions of adipose tissue. On the other hand, in severe grades of fatty degeneration the protoplasmic septa may disappear and the small droplets coalesce to form a large drop of fat. The origin of the fat present cannot be determined by microscopic examination; and in recent times the origin of fat from metabolic processes in the protoplasm of the cell has been vigorously denied. There is no doubt that fat may be produced in the organs from albuminous substances, and Virchow, in proof of this possibility, pointed to the occurrence of adipocere, in which fat may form in the muscles when cadavers or parts thereof remain for some time in a damp medium. It has also been found that maggots which have been kept in nutrient media consisting exclusively of albumin show an increase of fat in their bodies; but it is, nevertheless, difficult in cases of pathologic fatty degeneration to overcome the argument that the fatty increase is due to the increased introduction of fat from without and an inability of the cell to burn it up—in other words, to a kind of fat precipitation. For instance, in fat embolism fatty degeneration of the endothelial cells of the capillaries and of the leukocytes takes place (Benecke); and in the case of the fat emboli of puerperal eclampsia Ackermann demonstrated the occurrence of fatty degeneration of the glomerular epithelium. In these cases it is quite conceivable that the fat might be due to infiltration with fat circulating in the blood.

So-called fatty degeneration, or, better, fatty change or metamorphosis (Lukjanoff), also, has its physiologic prototype in the body. Whenever organs that have only a temporary importance are to be removed, nature employs as an intermediate process the conversion of the tissue into fat, in order to convert the building-stones of such parts into a readily transportable and absorbable material. Thus, for example, involution of the puerperal uterus takes place by a fatty degeneration of the enormously hypertrophied muscle-cells of the organ. The sebaceous glands and the mammary glands go through a process of fatty degeneration during the formation of their physiologic secretion. Thus the cells of sebaceous glands are packed full of fat-granules which coalesce and escape through the cell-body, while the latter collapses and disintegrates in the mammary glands; also the cells which are destroyed during secretion have to be replaced by new formation from the remaining cellular elements.

Under pathologic conditions fatty degeneration occurs chiefly when the oxidation processes in the body are disturbed—*i. e.*, in all those conditions in which the number of red blood-cells or the hemoglobin suffers a temporary or permanent diminution. Fatty degeneration accordingly occurs after severe hemorrhages and in local anemia, as, for example, from compression of blood-vessels. Thus, fatty degeneration of parenchymatous tissues always occurs in the neighborhood of a rapidly growing spheric tumor in such organs as the liver, brain, kidneys, etc., in the periphery of tumor nodes, in tubercles, gummas, and in echinococcus cysts; the parenchyma becomes anemic from the pressure of the abnormal growths, and oxidation is hindered. The great tendency to intense fatty degeneration observed in tumors of extraordinarily rapid growth, such as carcinoma and sarcoma, is attributed to insufficient blood-supply and consequent inadequate oxidation processes in these neoplasms. As a matter of fact, fatty degeneration is most pronounced in those portions which are farthest removed from the nutrient vessels. The extensive fatty degeneration which attacks the parenchymatous organs, the heart, and the muscles, in so-called pernicious anemia is generally well known.

Intoxications, in which the percentage of oxygen in the blood is diminished, are also followed by fatty degeneration; among these may be mentioned poisoning with carbon monoxid and pyrogallol. Widespread fatty degeneration of extreme intensity develops in poisoning by phosphorous, arsenic, antimony, bismuth, iodoform, carbolic acid, and in poisoning by many varieties of mushrooms. Bauer states that in phosphorus-poisoning there is an increased decomposition of albumin, with a diminution in the ingestion of oxygen and decomposition of fat. Finally, fatty degeneration frequently develops after the acute infectious diseases, the most familiar examples being diphtheria, small-pox, scarlet fever, and, in a lesser degree, typhoid fever and cholera. The fatty degeneration which attacks many of the organs in severe general jaundice, for example, in acute yellow atrophy of the liver, may also be mentioned.

In fatty degeneration the affected cells are crowded with fat-droplets. During the initial stages these fat-droplets are extremely minute, and sometimes have certain relations to the normal structure of the cell. It has been believed that the fat-droplets in the epithelial cells of the kidney and liver take the place of the disappearing Altmann granules, and it has, therefore, been believed that these elementary structures are converted into fat-droplets. In the heart muscle, for example, the small fat-droplets are seen to be arranged in regular rows in the direction of the muscle-fibres—that is, along the longitudinal striations. The transverse striation may be preserved during the initial stages; later, however, as the fatty droplets increase, it disappears. The nuclei are obscured, and cannot be recognized in severe grades of the condition even after being treated with acetic acid or with an alkaline solution, while in medium grades the fatty degeneration is sometimes rendered more distinct by adding these reagents, because the albuminous particles which are present with the fatty droplets are dissolved and the cells thus cleared. In the kidneys, when fatty degeneration is not very far advanced, the peripheral portions of the epithelial cells of the uriniferous tubules—that is, those portions nearest the membrana propria—are seen to be filled with minute fat-droplets (Plate 11, Fig. 3), while in the more degenerated portions, which generally include the so-called intercalated pieces, the cells present a diffuse infiltration with droplets; later the cells are cast off and occupy the interior of the membrana propria in the form of fatty epithelial casts, which often make their appearance as such in the urine.

Fatty degeneration is often observed in gland-cells,—*e.g.*, in the stomach, intestine, and pancreas. It is particularly common in the substance of the central nervous system after nutritive disturbances or the destruction of some of its parts. The nervous substance rapidly breaks down into an extremely fine, granular mass of fat-droplets which are taken up by contractile cells. The latter are partly leukocytes and lymphocytes and partly endothelial and ganglion-cells (Birch-Hirschfeld), which become loaded with fat-droplets and are known as granular-cells, and, when the fat-droplets disappear, as granular spheres.

Fatty degeneration may also attack connective-tissue cells. Thus in the medium-sized and large vessels affected with atheromatosis the yellowish, thickened patches on the intima contain large, stellate connective-tissue cells provided with outrunners, which are impregnated with whole rows of fat-droplets (Vol. I., Plate 10, Fig. 3). The connective-tissue cells in the cornea may become the seat of fatty degeneration in old age; the corresponding part becomes opaque and produces the so-called arcus senilis.

Finally, cellular and fibrinous inflammatory exudates may succumb to fatty degeneration. The absorption of pus, for example, is usually preceded by fatty degeneration of the pus-cells, and when such cells are accumulated in large quantities, as, for instance, in empyema, it is often impossible to find a single intact pus-cell, as all are closely beset with fat-granules. In some species of animals (rabbit) the pus-cells appear to possess a special tendency to fatty metamorphosis. If absorption of the water takes place at the same time, a condition is produced which is designated caseous. The dissolution of fibrin is accompanied quite frequently by the formation of large masses of fat-droplets which are evidently derived from the disintegration of the fibrin thread; this is seen in the resolution [autolysis—Ed.] of the fibrinous exudate in croupous pneumonia. By this means the exudate becomes emulsified and its conversion into an absorbable state is effected.

Fat, even when present in small and isolated granules, is readily recognized by its microchemical reactions. It is not affected by acetic acid and alkalies, but is readily dissolved in ether, benzine, and chloroform, after the tissue has been previously treated with absolute alcohol. All fat-containing tissues that have been preserved and imbedded in the usual way therefore show a complete absence of fat, and the spaces occupied by fat-drops are converted into vacuoles. Hence the fatty tissue in the usual, stained, permanent preparations always appears in the form of the well-known meshwork, the meshes of which correspond to the protoplasmic borders of the fat-cells. The smaller the droplets of fat which have been extracted by the treatment of the section, the smaller will be the corresponding vacuoles. When an organ the seat of marked fatty degeneration has been preserved in this ordinary way and is examined, the protoplasm accordingly represents a so-called frothy structure, the innumerable minute holes or cavities corresponding to the minute fat-droplets, and the threads that are visible between them to the remains of the protoplasmic septa. It is possible, however, to preserve the fat *in situ* by treating the tissue with osmic acid, which stains the fat black. After it has been treated in this way the fat resists many reagents which otherwise dissolve it rapidly, like ether and chloroform; while other substances, such as benzine, xylol, and toluol attack and dissolve fat stained with osmic acid. Fat can be demonstrated very satisfactorily *in situ* by the aid of sudan III. (an anilin stain); but the sections cannot, of course, be treated with fat-dissolving reagents, and must, therefore, be preserved in formalin solutions. Fat can also be stained with chinolin blue and alkanna tincture.

If fat remains anywhere in the body after the disintegration of the inclosing cells, it undergoes a definite transformation, resulting quite frequently in the formation of masses of cholesterin, which appear as the well-known, large, vitreous, rhombic plates, often with one corner broken off (*Atlas of Special Pathologic Histology*, Vol. I., Plate 10, Fig. 2), and are stained an intense red by sulphuric acid. Needle-shaped margarin crystals, arranged in the form of a brush or a stellate figure (*Atlas of Special Pathologic Histology*, Vol. II., Plate 75, Fig. 2), are occasionally seen in old fat deposits.

It is needless to say that the nuclei also present certain changes in fatty degeneration. They undergo both chemic and morphologic disintegration and ultimately disappear; but these phenomena will be discussed more in detail in connection with necrosis.

Glycogenic Degeneration. [Infiltration.—Ed.]

Glycogen, a normal constituent of the body, which was discovered in 1858 by Claude Bernard in the liver, and later demonstrated outside of this organ, in the muscles, *in Henle's loops* in the kidneys, in cartilage, in striated squamous epithelium, in the uterine epithelium, in the normal placenta, and especially in all the fetal organs, may be increased in pathologic conditions or may be found in situations where it does not exist normally. These conditions are included under the term glycogenic degeneration [infiltration—Ed.] It occurs as granules, fragments, or small spheres imbedded in the cells in the form of shining, homogeneous bodies. It is assumed that in the recent condition glycogen is diffusely infiltrated into the cells, and that the drops are formed only postmortem or as the result of manipulation. It is extremely soluble in water, and for this reason can be demonstrated only in very recent tissue immediately after it has been taken from the body, or in tissue that has been at once preserved in strong alcohol. The degree of solubility is not the same in all the tissues of the body: some organs are evidently able to preserve the substance better and for a longer time than others. Glycogen is everywhere distinguished by its ready solubility in saliva. When brought in contact with iodin, its color changes to a brown or brownish-red shade. A solution of iodin in gum arabic or of iodoglycerin is usually employed to preserve stained glycogen. Under pathologic conditions glycogen is found in the blood in diabetes mellitus, both outside of the cells and within the leukocytes, where it can be demonstrated in the form of minute droplets. It is also found almost constantly in the leukocytes in cases of suppuration, before the pus-corpuscles have broken down, in abscesses, in gonorrheal pus, in purulent urine, in the leukocytes of the pneumonic exudate, and in general leukocytosis. It is found particularly in the kidney in diabetes mellitus, at the junction of the medullary and cortical substances, and at the isthmus of Henle's loops. The epithelial cells appear glassy and swollen, and on the addition of iodin and gum arabic, large and small spheric, brown droplets become manifest.

Glycogen is also quite common in true neoplasms of various kinds, especially in chondroma, in rhabdomyoma, in tumors of the kidneys and of the testicles

PLATE 12.

FIG. 1.—**Amyloid Degeneration of a Small Splenic Artery** (Hemat.-eosin. × 300.): 1, Endothelial cells; 2, tunica media, converted into a homogeneous band; 3, adventitial cells.

FIG. 2.—**Amyloid Degeneration of a Vascular Knot in a Renal Glomerulus** (Carmin; van Gieson. × 260.): 1, Amyloid degeneration of glomerular vascular coils; 2, Bowman's capsule; 3, albuminous substance in the capsular space.

FIG. 3.—**Amyloid Bodies in the Lung in Chronic Indurative Pneumonia** (Alum-cochineal. × 160.): 1, Thickened alveolar septa; 2, cellular and hemorrhagic exudate in the alveoli; 3, concentrically lamellated amyloid bodies.

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all those neoplasms which are formed from young cellular material closely related to embryonal tissue. On the other hand, it is never found in the so-called infectious tumors or granulomas.

Amyloid Degeneration. [Infiltration.—ED.]

A number of degenerative processes in the body are accompanied by the formation of hyaline, glass-like substances. These substances may be formed within the cells, so that when the cell breaks down they are liberated, or they may represent external products of cells, or they may be dissolved and circulate in the blood as abnormal constituents, and under certain circumstances be deposited in the tissues. So far the chemic composition of these substances has never been quite positively determined; all that is definitely known is that they represent albuminous bodies, and the various forms of degenerations here referred to are, therefore, known as albuminous degenerations. Among them the most important is amyloid degeneration, which was first accurately described by Virchow and regarded by him as a formation of cellulose within the animal body [hence the name "amyloid."—ED.]. Before his time the process was generally known as "Verholzung" (Bonetus), or "bacony degeneration" (Rokitansky). Friedrich and Kekulé demonstrated the albuminous nature of amyloid substance, and in recent times it was discovered by

Tab.12.

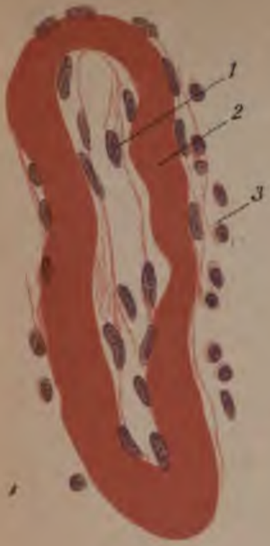

Fig.1.

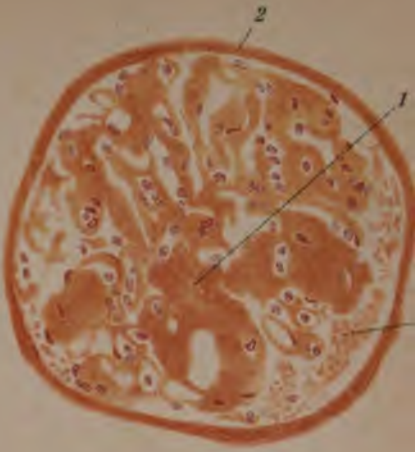

Fig.2.

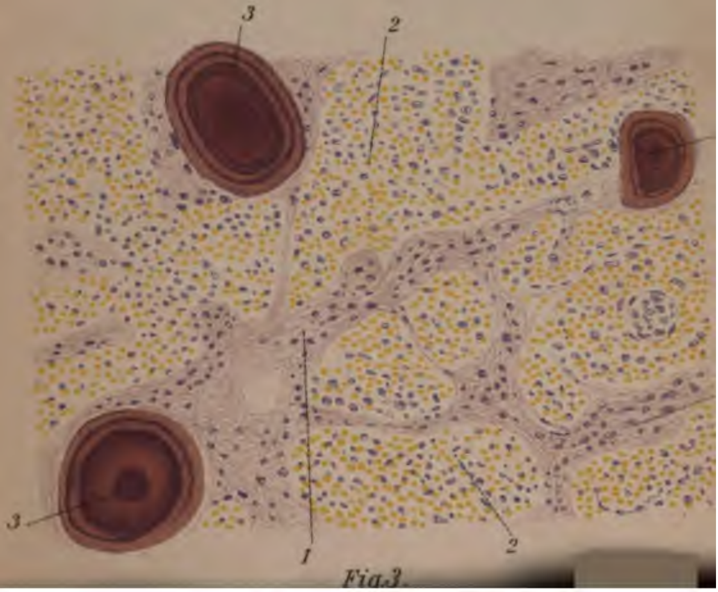

Fig.3.

Krakow that amyloid consists of a combination of an albuminous body with chondroitin-sulphuric acid.

The naked-eye appearance of amyloid substance, when extensively deposited in the tissues, is quite typical. It is a solid, dry, waxy, transparent, bloodless material. When present in abundance, it may be recognized with the naked eye by the iodin reaction, which is mentioned by Virchow. If the cut surface of an organ the seat of amyloid degeneration, after careful washing to remove the blood, is brought into contact with tincture of iodin (Lugol's solution), the amyloid portions take on a mahogany-brown or brownish-red color, forming a distinct contrast to the remainder of the tissue, which is stained yellow. It is with the microscope, however, that amyloid degeneration is most successfully demonstrated with the help of certain specific reactions, even in the initial stages and when the disease is very limited in extent. The most important of these reactions is that with iodin. By treating a recent specimen, or tissue hardened in alcohol, with tincture of iodin, after removing the blood as well as possible, until *all* the normal tissue is stained an intense straw yellow, the parts affected with amyloid degeneration appear first as brown, then brownish red, and later as red dots and lines. In severe cases, if the treatment with iodin is continued, amyloid often takes on a violet tint. The addition of dilute sulphuric acid to the preparation gives a dark violet or black stain; instead of sulphuric acid, chlorid of zinc may also be used. A number of anilin stains, when brought in contact with cut sections, yield typical reactions. Methylene-violet and iodin-violet stain the amyloid substance a ruby red; iodin-green and methylene-green give a reddish-violet color with the amyloid substance. What has been said about glycogen applies equally to amyloid substance—namely, the reactions are not equally distinct in every portion of the body. It may be mentioned also that amyloid gives the xanthoprotein reaction (yellow color with nitric acid); when pulverized, it is digested by the gastric juice; it is readily soluble in trypsin.

The amyloid substance may be diffused throughout the body or strictly localized in a certain region. Opinions have long differed in regard to the mode of its formation, as well as its distribution among the various tissues of the body that are subject to amyloid degeneration. The infiltration of the body or of individual vital organs with amyloid substance may be so intense as to cause the complete disappearance of the specific cellular constituents of the organ and work the greatest possible functional injury. It is evident from all we know of amyloid degeneration to-day that both its formation and its distribution are exclusively extracellular—that is to say, the cells of an organ are never attacked by the degenerative process, and all the changes they show are merely secondary. According to von Recklinghausen's view in regard to the formation of amyloid substance, a homogeneous material is extruded from the cells of the organs, and, coming in contact with the body-juices and indirectly with the blood, swells up like lumps of mucus. This maceration is attended by clumping and the formation of trabeculæ or reticular structures, and sometimes by the formation of membranes or tubes. According to this view, the process is a kind of coagulation comparable to the formation of fibrin. According to other authors, however, the formation of amyloid substance is due to the escape from the blood of an albuminous body, which is incapable of being further decomposed in the organs and is converted into amyloid substance by contact with chondroitin-sulphuric acid. It has also been believed that certain preliminary stages of amyloid material occur in the body, among which hyaline substance is the most important; there is no doubt that both hyaline and amyloid degeneration [change.—Ed.] are sometimes demonstrable in the same organ.

Amyloid change always begins in the connective tissue, more particularly in the vascular walls of the affected organs. This preference for the vascular walls suggested that the substance was derived from the blood; it is, however, the media, and not the intima, of the small *arteries that is first* attacked; the spaces between the muscle-cells are filled with glassy, translucent material in stripes, fragments, ribbons, and dots, which ultimately coalesce and later form a complete ring or cylinder around the vessel. The muscle-fibers are crowded to one side, compressed, and usually destroyed first, while the intima, or at least the epithelium, may persist for some time. Amyloid substance deposits itself in the tissue elements in the following order of frequency: smooth and striated muscle, connective tissue of the liver and kidney, spleen, lymphatic glands, suprarenal capsules, the villi of the intestines, stomach, uterus, and heart. Amyloid degeneration is never observed in the epidermis or in the glands of the skin, in the lungs, bones, or nervous tissue. Amyloid degeneration may also attack neoplasms more or less extensively, especially those which, like fibromata, are made up chiefly of connective tissue, which in itself possesses a tendency to the formation of homogeneous masses. Scars may also undergo amyloid degeneration.

In almost all cases of amyloid degeneration certain chronic disorders associated with a severe grade of anemia and the continuous loss of albumin are present and represent the indirect cause of the degeneration. Among these the most important are chronic tuberculosis of the lungs and of the bones and joints, chronic syphilis, suppurations in the intestinal canal, especially chronic dysentery, malaria, cachexia, and ulcerative carcinomatous neoplasms in the stomach and in the internal female genitalia. Amyloidosis is also observed in chronic nephritis, in chronic alcoholism, in leukemia, and in pseudoleukemia. In rare cases it is impossible to demonstrate a primary causal disease, but even in these cases the individuals are in a depraved state of nutrition from unfavorable conditions of life, or they are cases of senility. Several experimenters have succeeded in producing amyloid degeneration artificially in animals by administering pus taken from caries of bones (Birch-Hirschfeld), by repeated inoculation with living staphylococcus cultures, dead staphylococci, or with putrefactive material, or by keeping up suppuration for weeks at a time by means of irritants, especially turpentine

In regard to the histologic examination of the individual organs that are subject to amyloid disease, those which interest us most are the large parenchymatous organs.

In the *liver* it is almost always the so-called intermediary zone of the acini that is attacked. The substance is deposited in homogeneous lines between the endothelial tube of the portal capillaries and the cords of liver-cells; the linear masses coalesce to form larger bands, which gradually become thicker and increase the distance between the wall of the capillary and the liver-cell. By progressive thickening of these amyloid bands, which extend both toward the central vein and toward the peripheral zone of the acini, the blood-vessels and particularly the liver-cells are more and more compressed. The compression of the liver-cells goes on until they are reduced to narrow ridges and their continuity is broken at the points where the amyloid substance presents the greatest accumulation. At the same time they are usually attacked by profound fatty degeneration, which results from the interference with the oxidative processes. Ultimately the liver-cells may break down altogether in places, and the amyloid substance may form broad rings at some distance from the central vein, within which the endothelium may for some time continue intact and easily demonstrable, even when the liver-cells have been completely destroyed in many places. The process, of course, results in enlargement of the organ with increase of its consistence, and, owing to the compression of the blood-vessels, profound anemia of the tissues.

In the *kidney* the amyloid substance deposits itself in the muscularis of the small cortical arteries and especially within the glomeruli on the surface of their vascular coils. The latter are the first to show small, crescentic or spheric deposits, which inclose the vessels like cylinders and in transverse section appear as rings. Sometimes a single vascular coil undergoes degeneration while the rest remain quite intact, or the process may involve several of the coils at once and only a single one escape for a long time. *The deposition of* the substance within Bowman's capsules eventually leads to their obliteration, and a desquamation of the epithelial cells into the capsule takes place. The cells undergo fatty degeneration, are destroyed, and carried away in the urine; finally, in the last stages of amyloid degeneration, every vestige of a nucleus disappears and the glomerulus represents a mere hollow structure, containing a few sausage-shaped masses of a glassy material which gives the well-known reactions and which, by its arrangement, betrays its origin from the fragmented vascular coils. It is probable that fragments of amyloid may separate from the glomeruli and be washed into the lumen of the uriniferous tubules, for in kidneys the seat of higher grades of amyloid degeneration casts are sometimes found in the uriniferous tubules with a well-preserved epithelial lining, and giving the amyloid reaction. The amyloid substance may also deposit itself in the tunica propria of the uriniferous tubules. The amyloid bands, rings, and cylinders push their way in between the tunica propria and the desquamated epithelial cells, and, as they increase in size, compress the parenchyma, as in the case of the liver, and cause its destruction. Amyloid degeneration of the glomeruli and of the small arteries is regularly accompanied by fatty degeneration of the epithelium of the uriniferous tubules.

In the *spleen* the venous capillaries first fall a prey to amyloid degeneration. Later they are converted into broad, glistening homogeneous bands, with the endothelial cells projecting into their lumen. As the amyloid substance increases the pulp is compressed more and more and atrophies, the amyloid bands may coalesce, and often the follicles alone remain as mere circular gaps in the amyloid ground substance. The pulp becomes solid and presents a rough, glistening appearance (bacon-spleen, ham-spleen), and is exceedingly anemic. On the other hand, amyloid degeneration may develop chiefly within the follicles, the bands of amyloid substance attaching themselves to the reticulum. The lymph-cells are compressed and ultimately disappear altogether; and on the cut surface the amyloid substance displacing the Malpighian corpuscles stands out

PLATE 13.

FIG. 1.—**Amyloid Bodies in the Prostrate** (Hemat.-Eosin. × 230.): 1, Concentric amyloid bodies with distinct nuclei; 2, dilated glandular spaces in the prostrate; 3, desquamated epithelial cells.

FIG. 2.—**Amyloid Degeneration of the Kidney in Chronic Pulmonary and Intestinal Tuberculosis** (Iodin-green. × 280.): 1, Uriniferous tubules with desquamated epithelial cells; 2, metachromatically stained, vascular coils of a glomerulus in a state of amyloid degeneration; 3, intact epithelial cells in the vascular coils.

FIG. 3.—**Diffuse Amyloid Degeneration of the Spleen** (Bacon-spleen) (Hemat.-eosin. × 300.): 1, Follicles; 2, blood-vessels of the pulp, the walls of which have undergone amyloid degeneration; 3, pulp-spaces.

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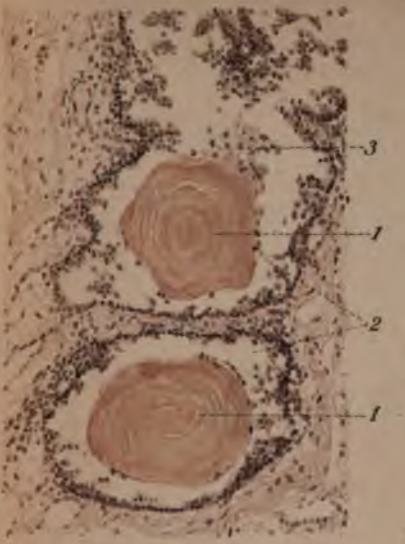
in transparent spheric masses which have been likened to boiled sago (sago spleen).

In the *heart* the amyloid bands are seen in the medium-sized and smaller arteries, subsequently spreading to the interstitial connective tissue; when very thick, they may compress the adjoining muscular tissue and cause it to undergo atrophy. In the fatty tissue the membranous capsules of the fat-cells in transverse sections appear as uniform rings, owing to the infiltration with amyloid substance. The lumen of these rings contracts more and more until the fat-drop finally disappears altogether and the entire fat-cell is converted into a spheric mass of amyloid. In the muscles the amyloid substance spreads chiefly in the internal perimysium and in the sarcolemma; the sarcolemma tubes undergo concentric broadening, the contractile substance of the sarcoplasm disappearing.

Amyloid degeneration is not always distributed equally throughout the body; it may be localized, as, for example, in the formation of tumor-like deposits in the conjunctiva, especially in trachoma-like proliferations; on the tongue and in the upper air-passages; in the larynx and trachea ["amyloid tumors."—ED.]. These local deposits of amyloid may later be invaded by giant-cells and undergo spontaneous dissolution, so that amyloid fragments are sometimes found imbedded within leukocytes.

Tab. 13.



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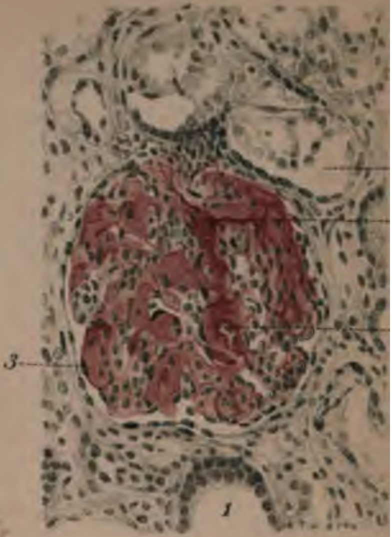

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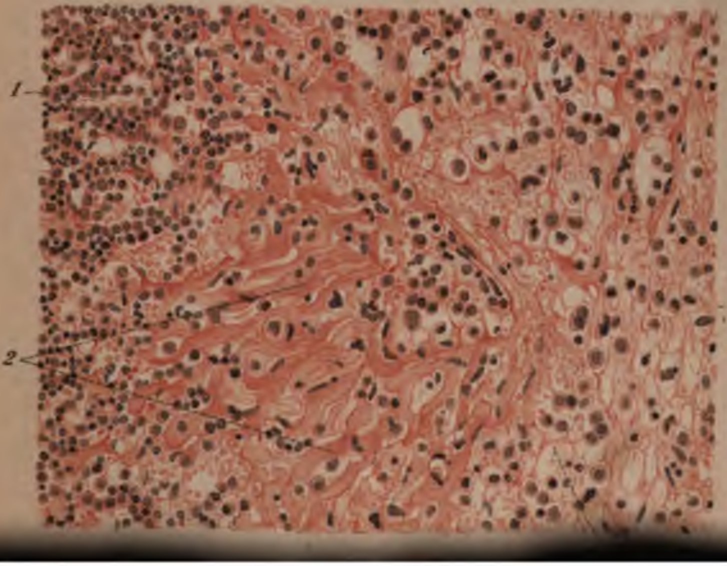

Finally, amyloid substance may be observed in the form of concretions in the body. The structures are circular, angular, or wavy in outline, and in cross-sections exhibit a distinctly concentric lamellation. They are observed chiefly in the central nervous system, especially in degenerated portions of the spinal cord and in the ependyma of the ventricles. In the prostate they may attain a great size and may even be visible to the naked eye in the form of brownish granules (Plate 14, Fig. 1). They also occur not rarely in the lungs (Plate 13, Fig. 3), usually in chronic inflammatory, indurative processes; within the remains of infarcts and in emphysema. All these structures are formed by the agglutination of cells, especially epithelial cells, as may be seen in serial sections of the prostate gland. The center of the formation may contain corpuscular elements, dead cells or nuclei, hematoidin crystals, and the like, which in some way have been included.

Among these amyloid bodies we distinguish the *corpora versicolorata* (Siegert), which stain brown, red, and violet when treated with tincture of iodin and sulphuric acid, and the *corpora flava*, which are stained a uniform yellow by tincture of iodin.

Mucoid Degeneration.

Mucoid degeneration finds its physiologic prototype in the normal formation of mucus in the mucous glands, on the mucous membranes, in the connective tissue of tendons, in bursæ and synovial membranes, as well as in Wharton's jelly in the umbilical cord. The subcutaneous cellular tissue of the fetus also contains a large quantity of mucus.

The presence of mucus is demonstrated by means of the mucin reactions; mucin is not coagulated by boiling: it is precipitated by acetic acid and dilute mineral acids, and redissolved in an excess of mineral acids. The substance is precipitated with basic lead acetate. It is distinguished from albumin also by the fact that it is not precipitated by ferric chlorid, copper sulphate, mercuric chlorid or silver nitrate, but, like genuine albumin, it

PLATE 14.

FIG. 1.—**Mucoid Degeneration of Carcinoma Cells in Gelatinous [Colloid] Carcinoma of the Stomach** (Hemat.-eosin. ×80.): 1, Intact epithelial cells; 2, stroma; 3, swollen carcinoma cells; the nuclei have been displaced toward the wall and the cells are filled with mucous spheres; 4, free mucous spheres; 5, remains of nuclei.

FIG. 2.—**Mucus-formation in a Papillary Cystadenoma of the Ovary** (Hemat.-eosin. × 625.): 1, Connective-tissue stroma; 2, tall cylindric epithelial cells; 3, the bases of goblet-cells; 4, the nuclei of goblet-cells compressed at their upper pole by spheres of mucus; 5, swollen external half of the goblet-cells; 6, free mucous spheres.

FIG. 3.—**Colloid Formation in a Parenchymatous Goiter** (Hemat.-eosin. × 627.): 1, Walls of glandular alveoli with well-preserved epithelium; 2, partially destroyed epithelium; 3, homogeneous colloid masses; 4, vacuoles within the latter.

FIG. 4.—**Colloid-formation in a Contracted Kidney** (Alum-cochineal-nigrosin. × 280.): Uriniferous tubules filled with colloid casts; 2, dilated and cystic uriniferous tubules containing large masses of colloid material; 3, epithelial remains of the uriniferous tubules; 4, vacuoles in the colloid masses; 5, nuclear remains imprisoned within the colloid material; 6, glomerulus.

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gives the xanthoproteid reaction. Mucin contains a small quantity of sulphur and nitrogen and is free from phosphorus. Some varieties of mucin are entirely free from sulphur. A body which is closely related to the latter form of mucin is known as *pseudomucin*; it is morphologically undistinguishable from mucin, being a stringy substance, but it is not precipitated by acetic acid. With hematoxylin mucous substances usually stain a pale grayish blue to intense blue. In the epithelium the formation of mucus normally, as well as pathologically, takes place through the agency of the so-called *goblet-cells*. These usually are club-shaped, the narrow extremity being directed toward the underlying tissue and the dilated mouth toward the surface. The formation of mucus takes place regularly in the upper half of the cells, which is directed toward the lumen of the corre-

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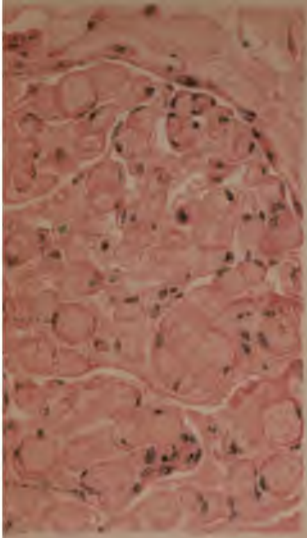

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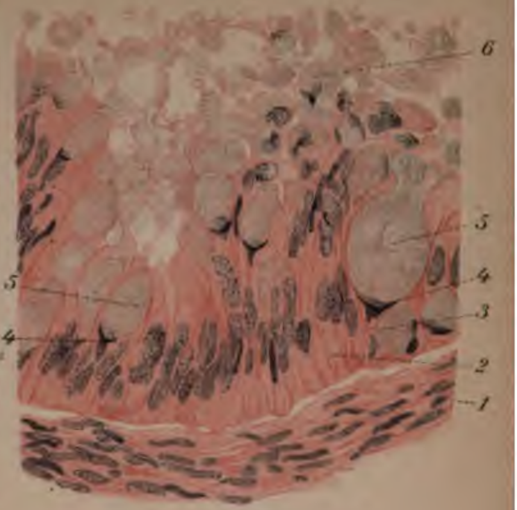

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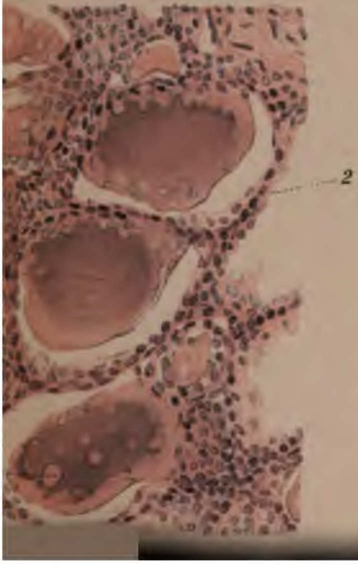

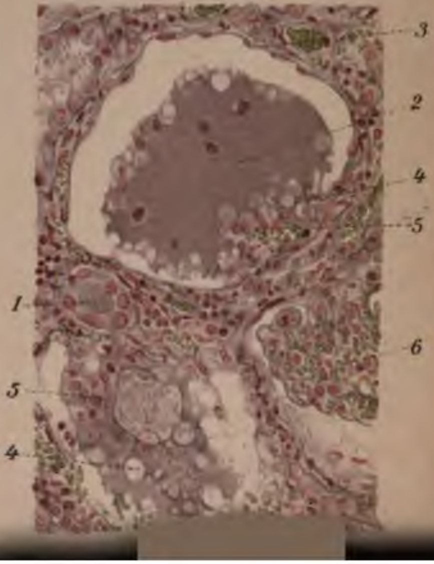

sponding canal. It would appear that some constituents of the nucleus are utilized by the cell in the formation of mucus. These portions, which escape from the nucleus and consist of achromatic substances, are known as *hyalosomes.* After their escape into the cell-body they become greatly swollen and ultimately give off spheric masses, which are always divided from the rest of the protoplasm in the cell-body by a sharply defined, peripheral borderline and are known as mucous spheroids. As a rule, the nuclei during this process of mucin production undergo a definite change,—*i.e.*, they are usually displaced toward the base of the cells; the pressure of the mucous masses causes a circular depression at the apex and a general flattening; sometimes a pale, delicate strip projects into the ball of mucus (Plate 14, Fig. 2). These intimate relations between the nucleus and the mucous spheroids recall the close chemic similarity of mucin and nuclein.

Ultimately the masses of mucus cause the surface of the cell to bulge, rupture takes place, and the spheres of mucus escape to the outside and deposit themselves as roundish structures or confluent, stringy masses on the surface of the mucus-producing epithelium. After their evacuation the cells coalesce and sometimes, but not always, die. It appears to be possible for the cell to be reconstructed from what remains of the protoplasm and of the nucleus; sometimes division of the nucleus takes place before the escape of the hyalosomes. In addition to the goblet-cells there are always other cylindric cells, in which mucoid metamorphosis has not reached so high a degree. It is probable that any epithelial cells may, under certain circumstances, be converted into a goblet-cell; thus, for example, in animals after experimental poisoning with pilocarpin a very copious formation of goblet-cells is sometimes observed.

In pathologic conditions the formation of mucus usually implies the genesis of goblet-cells, just as normally, except that production of mucus is much more active; the mucus-cells are closely packed in a small space and produce large masses of mucus. The processes described as catarrh are all characterized by this increase in the formation of goblet-cells in the affected mucous membranes. At the same time leukocytes accumulate and force their way through between the epithelial cells and enter the mucus. The leukocytes themselves may undergo mucoid degeneration after their death.

As in catarrh, so also increased formation of mucus may take place in a number of epithelial neoplasms through the agency of goblet-cells, especially in adenomata of the intestinal canal and cystic or papillary adenoma of the ovaries. In the latter organs enormous masses of mucus sometimes accumulate; but as these masses usually fail to give the acetic-acid reaction, they probably represent pseudomucin. In carcinomata, also, the parenchymatous cells of the tumor quite frequently undergo wide-spread mucous degeneration; the processes may even be primary, so that every epithelial cell from the beginning undergoes mucous metamorphosis (gelatinous [or colloid] cancer); or a secondary mucous degeneration of individual nests of epithelial cells may take place. The condition is usually accompanied by the formation of large cystic or balloon-like cells, within which the paraplastic mucoid mass is collected in the form of numerous spheroids, while the cell-protoplasm is reduced to a few delicate strands and threads, and the nuclei to narrow, crescentic, or sickle-shaped structures pressed against the cell wall (Plate 14, Fig. 1).

Mucoid metamorphosis is not by any means confined exclusively to epithelial cells. Under pathologic conditions it may occur in the connective tissue, converting the same into a gelatinous mass which shows the greatest likeness to Wharton's jelly in the umbilical cord. In this variety also the spindle-shaped connective tissue cells excrete mucous spheroids which collect between the cells like an intercellular substance and coalesce to form a homogeneous, mucoid, stringy mass. As a rule, the cells retain some organic connection, the cell-bodies anastomosing by means of club-shaped processes which gradually *widen* out. In this way the spider-web-like and radiating structures so characteristic of so-called myxomatous tissue are formed. Myxomatous degeneration of subcutaneous connective tissue is sometimes found extensively in cases of congenital absence of the thyroid gland, in atrophy of the gland, or after its complete operative removal. This condition, which is associated with other degenerative symptoms in the nervous system, is designated *myxedema* (*cachexia strumipriva*). Circumscribed myxomatous degeneration of connective tissue may occur. In advanced age myxomatous degeneration is sometimes observed in fat, cartilage, bone, and even in the marrow of bone. It is, of course, attended by considerable diminution in the consistence of the respective organs.

In order to demonstrate the existence of true mucous degeneration it is necessary to prove by chemic means that the intercellular substance really consists of mucin. Very frequently the swelling of a tissue from the accumulation of edematous fluid is erroneously designated mucoid degeneration. The only change here, however, is a more extensive serous infiltration of the tissues, forcing the cellular elements of the connective tissue apart, and thus histologically often simulating mucoid tissue.

Mucoid metamorphosis is often observed in connective-tissue neoplasms. Myxoma is a tumor which consists exclusively of mucoid tissue. Fibromata and chondromata may also undergo mucoid degeneration, and finally epithelial tumors, especially carcinomata, may present circumscribed myxomatous degeneration confined to the connective-tissue stroma.

Colloid Degeneration.

The term colloid is applied to material which macroscopically appears as a brownish, transparent, tenacious, and sticky substance, of the appearance and consistence of half-hardened glue; hence the name colloid, from *colla* = glue. But little is known in regard to the chemic nature of the substance [or substances.—Ed.] except that it is to be regarded as a normal product of the glandular alveoli of the thyroid gland and has certain definite relations to the active principle of this gland, iodothyrin. Outside of the thyroid gland colloid occurs normally in the hypophysis of the cerebrum, in the seminal vesicles, in the prostate gland, and in the suprarenal bodies.

Colloid is absolutely insoluble in hot and cold water as well as in alcohol and ether. When it is boiled with water, it does not yield glue. From mucin it is distinguished chiefly by its behavior with acetic acid, which first causes it to swell and then dissolves it completely. It is also completely dissolved by weak hydrochloric acid and it swells in alkalis. The xanthoproteid reaction is positive; the tinctorial reactions of the substance are variable.

Under pathologic conditions colloid may be produced in great excess in those organs in which it occurs normally, or it may be produced in organs which do not normally harbor the material. The former condition is seen in the thyroid gland in so-called *colloid goiter* (*struma colloides*). The glandular alveoli are greatly dilated and contain spheric masses of gelatinous, colloid material, which may attain the size of a pea. The entire gland enlarges greatly and sometimes gives rise to alarming pressure-symptoms in neighboring structures. As the result of pressure of the accumulated colloid masses, the epithelium in many of the alveoli appears low, flat, and atrophic. The spheres of colloid in transverse section look like homogeneous hyaline discs, except for small, cyst-like vacuoles in the marginal portions. Sometimes desquamated epithelial cells or wandering leukocytes are found in these vacuoles. In the relatively normal portions of the gland, where the cavities are still small, the increased colloid formation is readily recognized. The process must, indeed, be regarded as the result of a cellular metamorphosis. The colloid substance, like mucin, is produced in the form of spheroids in the peripheral half of the cell directed toward the lumen of the alveolus; after its escape from the cells it forms a homogeneous mass, and on coagulation assumes the *well-known*, semisolid, glue-like consistence. In the kidneys, colloid formation occurs chiefly in chronic inflammatory processes, when, owing to the extensive connective-tissue formation, individual uriniferous tubules or groups of tubules are isolated from the surrounding glandular tissue. Within the lumen of these tubules, or more rarely within the lumen of Bowman's capsules after the glomerular coils have been destroyed, are found masses of homogeneous substance with numerous vacuoles in the marginal zones (Plate 14, Fig. 4). These vacuoles sometimes contain desquamated cells or débris of cells, also single nuclei, and occasionally red blood-cells. Some of the uriniferous tubules may be entirely occluded by the colloid spheres or cylinders. As the colloid masses grow the occluded uriniferous tubules may form cysts of the size of a cherry and projecting above the surface.

Hyaline Degeneration.

According to von Recklinghausen's definition, the term hyalin is applied to a body of albuminous nature which is distinguished from the substances described in the foregoing, to which it is related, chiefly by its appearance, its homogeneous character, and its high refractive power. It has already been stated, in connection with amyloid degeneration, that hyaline degeneration is sometimes associated with it, and from this association it has been argued that hyalin may occur as a preliminary stage of amyloid; but amyloid degeneration is not by any means always preceded by hyaline degeneration. The tinctorial reactions of hyaline substance do not coincide with those which characterize amyloid material; the most important—that with iodin—is absolutely negative with hyalin. The substance is not coagulated by acids—not even by strong mineral acids. It remains unchanged in water and salt solution, as well as in alcohol and ether. It dissolves in ammonia. Chemically, hyalin is difficult to characterize, and the substance is even less definite as a chemic body than amyloid and colloid material. At all events hyalin is also an albuminous body, but it is probable that the term hyaline substance, as it is used now with our present

PLATE 15.

Fig. 1.—**Hyaline Degeneration in a Glomerulus and Hyaline Casts in Chronic Nephritis** (Hemat.-eosin. × 280.): 1, Vascular coils of a glomerulus in a state of hyaline degeneration; 2, initial portion of an uriniferous tubule with desquamated epithelium; 3, uriniferous tubule; the epithelium is almost entirely desquamated and degenerated; 4, hyaline casts within the same.

Fig. 2.—**Hyaline Degeneration of the Connective Tissue in a Corpus Fibrosum Ovarii** (Hemat.-eosin. × 280.): 1, Ovarian stroma; 2, blood-vessels in cross-section; 3, connective tissue the seat of hyaline degeneration; 4, connective-tissue nuclei.

PLATE 16.

Fig. 1.—**Hyaline Degeneration of Glomeruli in an Organized Renal Infarct** (Hemat.-orange. × 67.): 1, Newly formed connective tissue; 2, constricted remains of uriniferous tubules; 3, a normal glomerulus; 4, fibrous, spheric masses representing the former glomeruli, with hyaline marginal zones.

Fig. 2.—**Hyaline Fibrin from a Diphtheric Pseudomembrane of the Epiglottis** (Alum-cochineal; Weigert's fibrin stain. × 745.): 1, Hyaline bridge of fibrin; 2, hyaline fibrin in thick clumps; 3, nuclei of necrotic epithelial cells; 4, hyperchromatosis of the nuclear walls of the cells.

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knowledge, embraces a number of substances of different chemic composition. Tinctorially, hyalin is distinguished by its marked affinity for the acid anilin dyes—eosin, orange and acid fuchsin; it also takes a deep stain with carmin and picrocarmin. Hyalin occurs in the body under a great variety of conditions, and evidently originates from a variety of parent substances. In the first place, a distinction is to be made between hyalin of intracellular and hyalin of extracellular origin.

The intracellular hyalin is usually subdivided into epithelial and connective-tissue hyalin, according as it originates or is deposited in epithelial or in connective tissue. In the former case the cell protoplasm or parts of it, under the influence of some unknown agent, are converted into a hyaline substance, which escapes fully formed from the cells; the term secretory-degenerative

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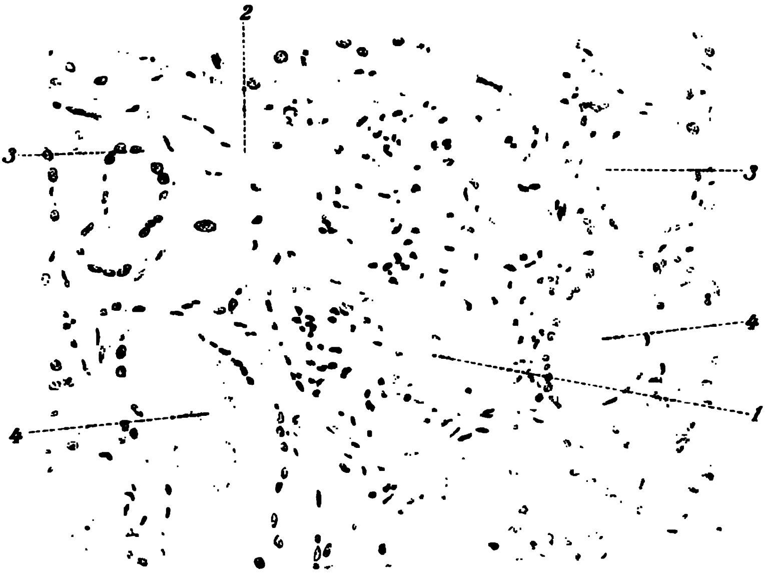

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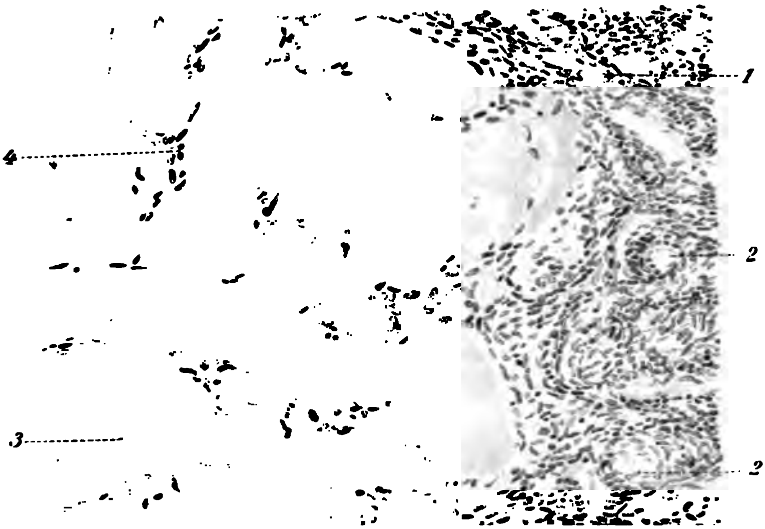

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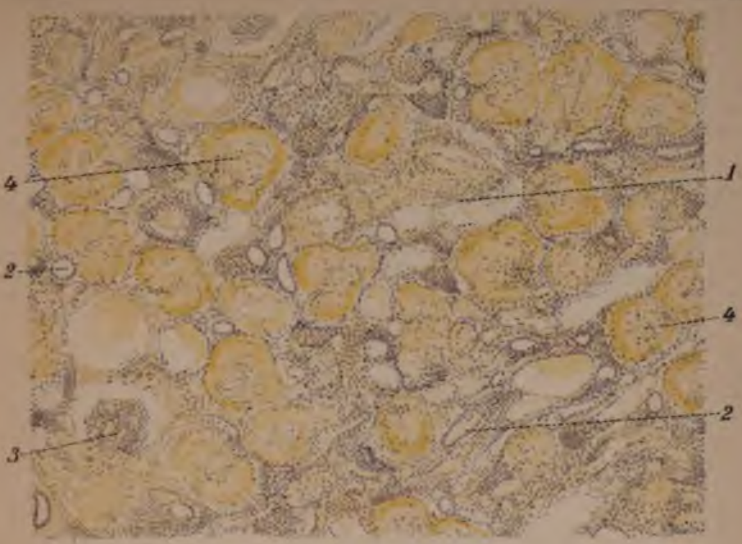

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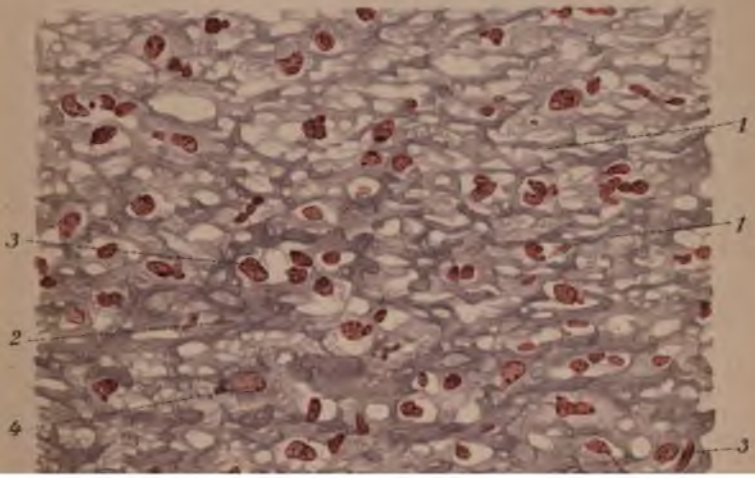

hyalin is accordingly used. For example, in the kidneys in the form of spheric and cylindric deposits, this variety of hyalin occurs after long-continued degenerative processes in the epithelial cells. The dilated uriniferous tubules, which have lost part of their epithelial lining (Plate 15, Fig. 1), are found filled with an almost homogeneous mass, which takes a deep stain with acid-fuchsin and the margin of which may contain a few isolated cells or débris of cells. Much more frequently hyalin is seen where connective tissue has been newly formed or a preëxisting connective tissue has undergone sclerotic changes; the connective-tissue fibers are unrecognizable and their places are filled by glistening fragments or convoluted masses which often attain a considerable width. The connective-tissue cells and the spindle-shaped nuclei have either disappeared altogether or are found scattered or arranged in chains between the hyaline masses. In the end the hyaline foci form hard, dry, glistening, spheric masses and fragments which project like rubber from the cut surface and even to the naked eye offer a certain resemblance to caseous nodules, a resemblance that is confirmed by microscopic examination. It is found, however, that the substance stains more deeply with the acid anilin stains and the homogeneous, glistening appearance also contrasts with the finely granular structure of cheesy foci.

This hyaline degeneration, or, to use a better and perhaps more generally descriptive term, "homogenization," of connective tissue frequently takes place in the endocardium, especially in the valves, the connective tissue of the intima of the large blood-vessels, in cicatricial tissue in the subcutaneous cellular tissue and in the cornea, in the corpora fibrosa of the ovary, which eventually fill the cavity of the ruptured Graafian follicles, and in connective-tissue scars which develop in various organs as the result of organization of infarcts. In the ovary the peculiarly interlaced and twisted masses of hyaline material are found in the immediate neighborhood of the cellular stroma of the organ; sometimes a few strands of connective tissue with cells and nuclei are found here and there among the

FIGURE III.

Hyaline Degeneration in the Glomeruli of an Old Renal Infarct (× 280.): 1, Uriniferous tubules; 2, remains of glomeruli; some of the coils still contain red blood-corpuscles; 3, Hyaline connective tissue in the marginal zones.

FIGURE VI. (Page 103.)

Uric Acid Infarct of the Kidney in the New-born. (Freshly isolated uriniferous tubules from the medullary substance, partially filled with spheric and nodular concretions (× 280).

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hyaline masses (Plate 15, Fig. 2). The similarity to caseous degeneration is sometimes exceedingly marked, especially as true disintegration and gradual dissolution of the nuclei in the hyaline tissue take place. Tuberculous lymph-glands usually contain an abundance of hyaline material produced by degeneration of the connective tissue. In the neighborhood of the cheesy or calcareous focus the reticular meshwork appears greatly thickened and represents glistening or sausage-shaped bodies, fragments, bands, and folds of material, among which the lymphadenoid tissue may be completely lost, so that both microscopically and macroscopically the impression of cheesy degeneration may be obtained at the first glance (Vol. I., Plate 16, Fig. 1).

In the scars after infarcts the homogenization of connective tissue is also attended by progressive destruction of the cells and nuclei. In organized infarcts of the kidney the sites of the glomeruli which have been destroyed are occupied by spheric accumulations of hyaline anuclear connective tissue, which look like little shining balls (Plate 16, Fig. 1). Sometimes the hyaline metamorphosis of the concentric connective-tissue layers in Bowman's capsule are readily recognized as it spreads from the periphery inward; the centers, which still contain some of the cells and nuclei, may be completely surrounded by these hyaline rings (see Fig. III., 3).

Weigert assumed that extracellular hyalin was due to a coagulation process, while von Recklinghausen derives the substance from cell protoplasm, especially from the

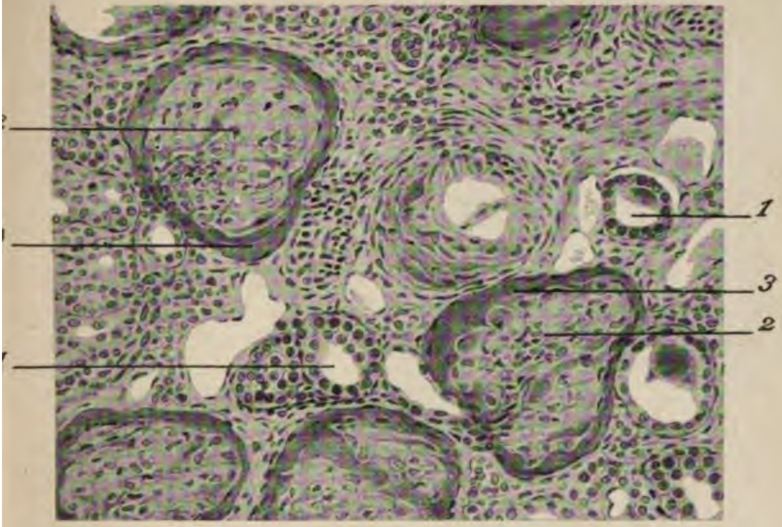

Fig. III.

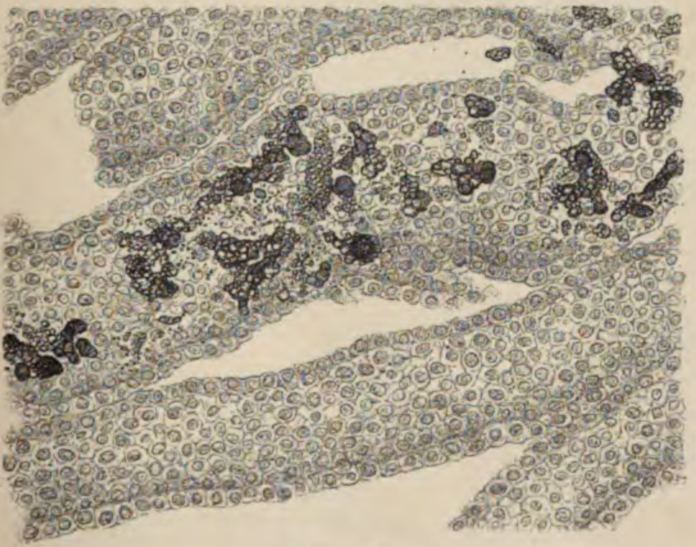

Fig. VI.

white blood-cells, and possibly from the endothelium of blood-vessels. As a matter of fact, in many cases the development of extracellular hyalin, which has been designated coagulation-hyalin, appears to be in some way related to fibrin; for it is observed either in association with fibrin or develops from true fibrin. Again, two larger groups may be distinguished—hematogeneous and conjunctival [connective tissue.—Ed.] hyalin. The former occurs as hyaline thrombi, usually in smaller vessels, especially capillaries, diphtheric inflammations of mucous membranes, in hemorrhagic pulmonary infarcts, in foci of croupous inflammation of the lungs, in the glomeruli, and in acute interstitial nephritis. In these cases the blood-vessels are completely occluded by homogeneous, glistening, sausage-shaped masses, the endothelial cells for the most part being destroyed (Plate 15, Fig. 1). As the result of hyaline thrombosis in the glomeruli the epithelium is cast off and swept away through the uriniferous tubules, so that hyaline masses are often found within Bowman's capsule entirely stripped of cells. These hyaline thrombi are also sometimes found in the liver in eclampsia, in the cerebral vessels in chorea, and in the capillaries of the skin in burns, and after death from freezing.

In exudative processes the formation of hyaline substance may be observed from the very beginning in many cases; in pseudomembranous (diphtheric and diphtheroid) inflammations associated with necrosis fibrin may be excreted in the form of interlacing, knotted bands and ribbons of varying width (Plate 16, Fig. 2). Sometimes part of the fibrin presents the well-known, delicate, fibrillar arrangement, while the portions which project into the tissue at once assume the appearance of a network of hyaline trabeculæ. Sometimes the fibrin threads later coalesce with one another to form conglomerate masses; especially in advanced stages of organization of fibrinous deposits, rounded masses, and fragments, which exhibit the morphologic and tinctorial features of hyalin, are seen on the surfaces of serous membranes, sometimes surrounded by granulation tissue or fully formed connective tissue (compare Plate 36, Fig. 2). In fibrinous thrombi a similar clumping and homogenization of the fibrin threads sometimes take place, and the entire mass appears uniformly glistening and fragmented—the so-called coagulation hyalin.

Hyalin also appears to represent a peculiar kind of local death of tissue in which albuminous substances undergo coagulation under the influence of the plasma. Thus hyalin is often observed in tubercles in association with a scanty amount of fibrin and extensive caseous necrosis. A similar origin must be assumed in the case of the hyaline substance which occurs in the so-called "waxy degeneration" of striated muscles. Scattered among the masses of hyaline substance are seen intact muscle-bundles and glistening, homogeneous bands, or minute spheres arranged in chains. Von Zencker was the first to describe this "waxy degeneration" in the abdominal muscles in typhoid fever; it is also observed in many other infectious diseases.

Finally, hyaline degeneration is often observed in many varieties of tumor, especially endothelioma and angiosarcoma. The hyaline substance in these tumors is often arranged in the form of cylindric tubes or casts surrounding the vessels, and these tumors have been called cylindromata.

[Concerning the occurrence, significance, and nature of circumscribed intracellular and extracellular masses of hyalin, found in inflammatory and proliferative lesions of various kinds and sometimes interpreted as parasites, see *American Text-Book of Pathology.*—Ed.].

Calcification and Petrifaction.

Calcium occurs naturally in the human body in the form of carbonate and phosphate. The bones of the skeleton are so intimately and uniformly infiltrated with the calcium salts that it is impossible to distinguish any structure in its deposition. Under pathologic conditions oxalate and phosphate of calcium, as well as combinations with the fatty acids, occur in addition to the carbonate and phosphate. But the union of the calcium with the cellular elements or the corresponding intercellular substance of the tissue in which it is deposited is not, as a rule, so intimate, the lime appearing usually in the form of variously sized granules, either spheric or angular in shape.

Calcification finds its physiologic prototype in ossification. It is first observed as a granular infiltration of the cartilage; the ground-substance of the cartilage, as well as the cell-capsules, undergo impregnation with lime salts after a peculiar preliminary rearrangement of the cartilage cells. Later on lime salts are also deposited in the lime-free osteoid ground-substance of bone.

Pathologic calcification may originate in one of two ways: either the calcium is deposited in the form of amorphous spheres and granules or in the form of large, nodular bodies which, when deposited in the intercellular substance or in cavities, are designated as *concretions*. These concretions also have their physiologic prototype in the so-called "brain-sand" or *acervulus cerebri*, spheric or mulberry-shaped granules, visible to the naked eye, which infiltrate the tissue of the pineal body and the venous plexuses in the cerebral ventricles.

Morphologically, the deposition of lime may occasionally be mistaken for fat-droplets; grains of calcium, however, are distinguished by the fact that they are less refractive, more irregular in shape, and present a dull sheen. In direct illumination with the diaphragm entirely closed the dull, whitish appearance of the granules is especially characteristic. On the addition of acids the calcium deposits are dissolved and the presence of calcium carbonate reveals itself by the formation of bubbles of carbon dioxid. When the calcified masses are treated with pure sulphuric acid, crystalline calcium sulphate is formed, the gypsum crystals appearing in the form of delicate needles, which are frequently arranged in the form of a brush or in a stellate manner. (See Fig. IV.) This reaction is quite characteristic, and should be performed to demonstrate the presence of pathologic calcification. When calcium salts have been dissolved and have entered the body-juices they do not give this reaction. With hematoxylin, especially Delafield's solution, calcareous masses stain an intense blue, not unlike nuclear chromatin, which is the only other substance that takes a similar stain with hematoxylin.

The calcium is deposited either within the cells, and may completely fill the body of the cell in the form of exceedingly fine dust; later the individual grains may coalesce to form larger particles, which eventually may be liberated by the breaking-down of the cells. Or the calcium may be deposited from the beginning in the interstitial substance outside of the cells.

The cause and true nature of calcification are subjects about which we still know very little. It may be that it depends upon a precipitation of calcium salts which circulate in the body-juices and have their origin either in the calcium introduced with food or in the breaking-down and solution of preëxisting calcium in the skeleton. It is also conceivable that calcium salts are deposited in cells or interstitial substance as the result of changes in the condition necessary for their remaining in solution. The former process is to be regarded as a precipitation of imported masses of calcium, while in the latter case it would be justifiable to speak of a true calcareous degeneration. Wherever pathologic calcification takes place in the body it is preceded by local death at the site where the calcium is precipitated. At all events, the nuclei invariably disappear before particles of calcium accumulate in large masses. In calcified carcinomata Marchand, however, has observed division of the nuclei in cells with beginning calcification, but it is fair to assume that the calcified parts are irrevocably lost to the body and cease to take part either in metabolism or in functional processes.

The occurrence of calcification in the body is extremely variable, and its pathologic significance also varies greatly in accordance with its distribution, its extent, and the rapidity with which it is formed.

1. The greatest similarity to physiologic calcification

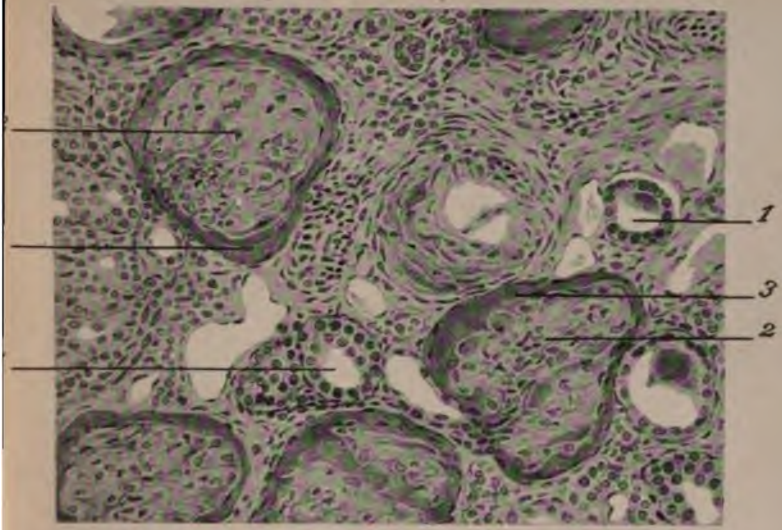

Fig. III.

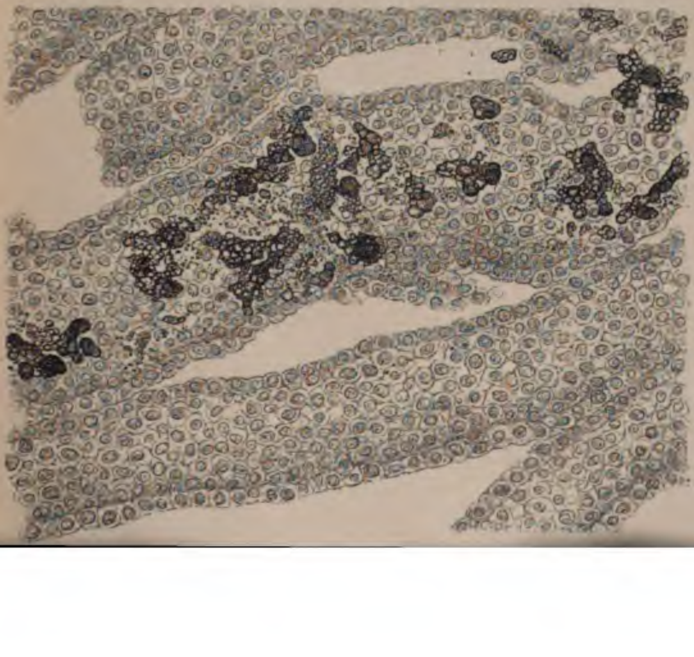

PLATE 17.

FIG. 1.—**Calcification of Renal Epithelium in Acute Bichlorid-of-Mercury Poisoning** (Five days) (Delafield Hemat. × 300.): 1, Uriniferous tubules showing desquamated epithelial cells, which for the most part are filled with granules of calcium; 2, necrotic epithelial cells without calcium; 3, intact tubular epithelium.

FIG. 2.—**Calcification in the Wall of the Aorta in Arteriosclerosis and Atheromatosis** (Hemat.-eosin. × 42.): 1, Thickened intima; 2, muscular coat; 3, adventitia; 4, sclerotic newly formed connective tissue of the intima; 5, calcareous masses in the intima, forming a communicating system of spicules; 6, cavities in the connective tissue, due to degeneration, filled with fat and masses of detritus; 7, blood-vessels that have grown into the media and intima from the adventitia.

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tion appears in the elastic fibers, and the effects of compression and displacement become noticeable in the muscle-fibers. Deposits of lime sometimes form large circular or semicircular figures, without necessarily causing marked changes in the width of the lumen or in the structure of the rest of the vessel-wall. Such arteries, however, are converted into rigid tubes without a vestige of their former elasticity, and, therefore, necessarily affect the action of the heart. Circumscribed calcification of the glomeruli may be found in the kidneys of old people, without any other changes in the parenchyma except a uniform atrophy of the cortex, which, however, is not attended by any marked increase of connective tissue. Sometimes in old age the straight uriniferous tubules in the pyramids present calcification in the form of fine, radiating lines which are especially prone to surround the openings of the connecting tubules in the cribrum. These lines consist of calcium carbonate and calcium phosphate, and to guard against mistakes must be carefully distinguished from urates, especially in this situation.

2. Abnormal deposition of calcium salts also occurs in the thymus gland during the period of its involution, especially if the latter is delayed; it involves the so-called Hassall's corpuscles, which are converted into glistening *spheres of* lime.

Tab. 17.

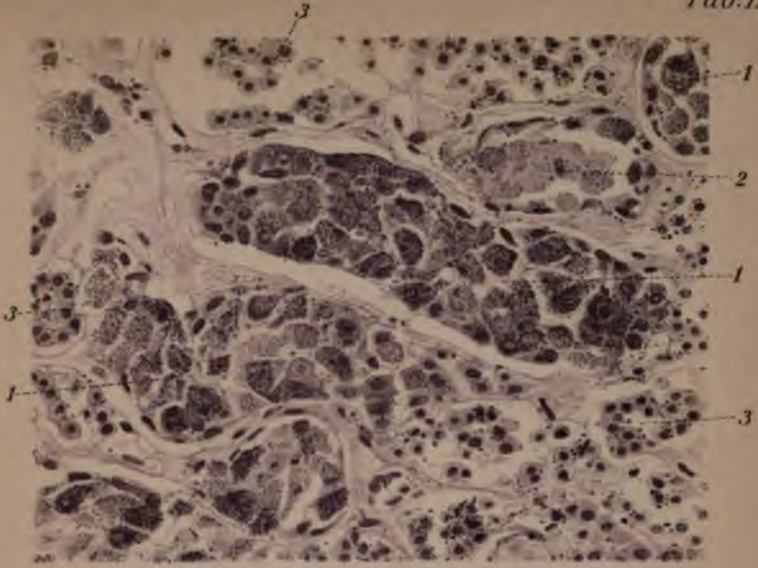
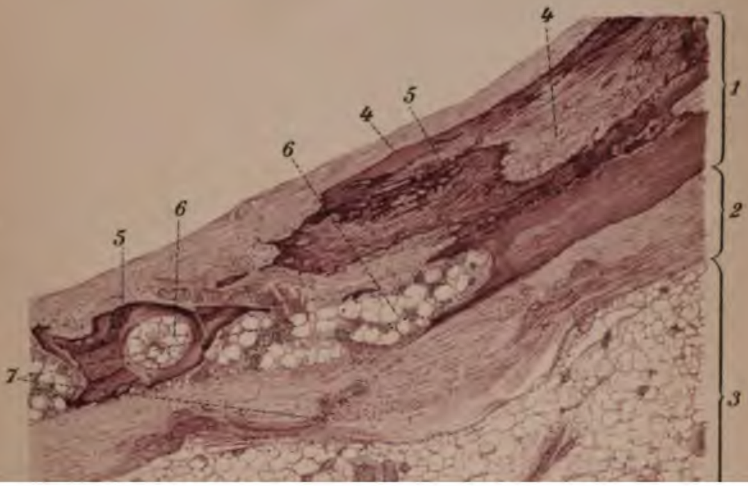


Fig. 1.



3. Pathologic deposition of calcium salts in the tissues is frequently observed in the various forms of nutritive disturbances. The latter appear to favor the deposition of calcium in a high degree; for whenever nutritive disturbance in a cell-complex has gone so far as to lead to cell-death, calcification is always possible, although it does not necessarily take place. Why in one place calcification occurs rapidly and in another place it never takes place at all is a question about which we are still in the dark. Processes that lead to coagulation necrosis appear to render the cells subject to a secondary deposition of calcium salts which sometimes takes place very rapidly; thus, in the case of the rabbit, for example, a temporary ligation of the renal arteries, lasting not more than two hours, may be followed by coagulation necrosis of the tissues within the next twenty-four hours, and by extensive calcification of the renal epithelium within the next few days. It is conceivable that the calcium present in solution in the blood is retained by those cells which have been severely damaged or killed and rendered unfit for their normal function. These forms of calcification of rapid development must be carefully distinguished from those which occur late in fully developed infarcts of various organs and which will be discussed shortly.

4. Extensive calcification sometimes takes place, especially in the kidney, within a few days after acute intoxications. This is characteristic of bichlorid-of-mercury poisoning, although even in these cases calcification often does not take place, while in other cases, which result fatally in the same time, the calcification may be extensive. In addition to bichlorid-of-mercury poisoning, intoxication with aloin, bismuth, iodoform, lead, copper, oxalic and chromic acid when given experimentally, or, as occasionally happens, when taken accidentally, is followed by calcification of the renal epithelium. The picture of acute calcification of the kidneys (Plate 17, Fig. 1) is exceedingly characteristic. The organ presents the appearance of a high grade of degeneration throughout the entire cortex. The epithelium is swollen, many cells are loosened

FIGURE IV.

Calcification of Renal Epithelium in Bichlorid-of-Mercury Poisoning (Frozen section. After the addition of sulphuric acid. × 280.): A few bubbles of gas (carbon dioxid) and large masses of needle-shaped crystals of calcium sulphate (gypsum reaction) are seen, arranged in bundles and radiating figures.

FIGURE V.

Calcified Epithelioma of the Skin (× 300. Specimen of Dr. Chilesotti): 1, Squamous epithelial cells with intact nuclei; 2, epithelial cells showing calcification around their margins; 3, completely calcified epithelial cells; 4, vascular stroma.

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from the basement membrane, cast off into the lumen of the uriniferous tubules, and densely packed with fat-droplets. The nuclei in most of the cells are unrecognizable. Even in recent, teased preparations irregular, angular, and circular fragments and granules of varying sizes, presenting the typical whitish sheen with direct illumination, may be seen in the necrotic epithelial cells. The addition of sulphuric acid, which is attended by the development of bubbles of gas, is immediately followed by the appearance of the needle-shaped gypsum crystals (Fig. IV.). In permanent-stained preparations the distribution of this process becomes even more definite, for the lumps and fragments, which stain an intense blue with hematoxylin, in many places appear to fill the desquamated epithelial cells completely. The convoluted tubules of the second order appear to be especially affected; not a single cell with a tingible nucleus may be found, and the epithelial cells, which are cast off in large numbers, in places form actual calcareous casts in the interior of the membrana propria. The epithelium of the glomeruli generally escapes calcification; but, as a rule, these structures are invaded by fatty degeneration. The straight uriniferous tubules contain granular, calcareous, epithelial casts, although their own epithelium is usually intact at the time of death.

5. An extensive deposition of calcium salts, especially phosphate and carbonate, is sometimes observed in the

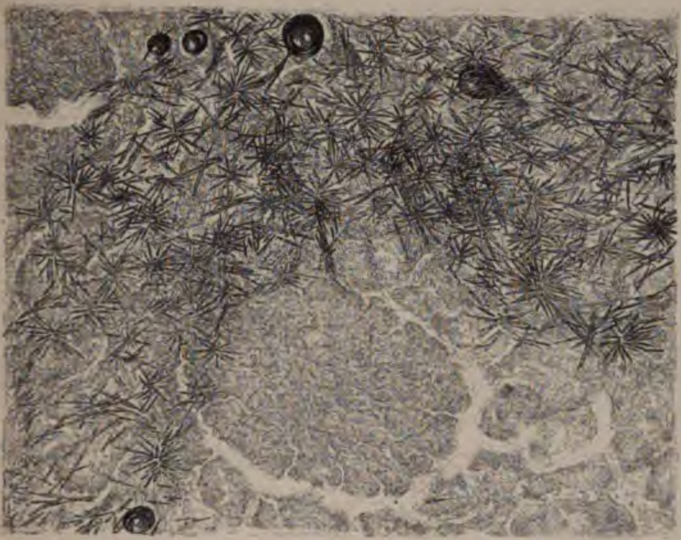

Fig. IV.

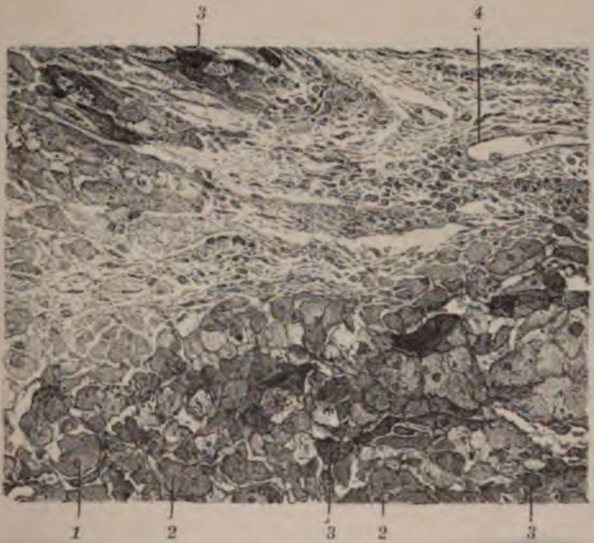

Fig. V.

interior of granulomatous growths after they have fallen prey to caseous necrosis. Tubercles and gummata are particularly apt to collect large masses of calcium at their centers after the process of necrosis has been completed. The line appears first in the form of fine granules and dust-like particles within the cheesy and necrotic tissue. Later the particles coalesce to form compact, nodular concretions of various sizes, resembling calculi, and the cheesy, tuberculous infiltrate undergoes complete petrifaction. If the tuberculous process is arrested at the margins, and at the same time calcification progresses until it has reached the connective-tissue capsule with which these old tuberculous foci are usually surrounded, spontaneous recovery from the tuberculous disease may take place. The process is observed most frequently in the apices of the lungs, and especially in certain groups of lymph-glands, chiefly the peribronchial. Sometimes the lesion is replaced by a dry, chalky, or mortar-like focus consisting of amorphous, fragmented masses of lime. In many animals, especially neat cattle, this deposition of calcium salt occurs regularly in tuberculosis after central caseation has begun in the granulomata. In these cases calcification is not complete, for the eruption of tubercles continues around the margin of the focus after the center has become calcified. The attempts to force this calcification, which is so desirable for the cure of the tuberculosis, by administering large quantities of calcium with the food, have not yielded any satisfactory results so far. These experiments would seem to show that the calcium deposited in cheesy and necrotic vessels is not derived from the calcium salts dissolved and circulating in the blood, but is the result of a calcareous metamorphosis of the cheesy and degenerated tissue. Extensive calcium degeneration sometimes occurs also in syphilitic granulomata, the deposits, so far as their morphology is concerned, being precisely similar to those seen in tuberculosis.

6. In the central nervous system calcification of the essential tissue elements often takes place in a short time after certain definite nutritive disturbances or traumatic

accidents, the neurocytes chiefly being attacked. The latter exhibit marked shrinking and the presence of closely packed, glistening, calcareous granules arranged in orderly rows and sometimes extending into the processes of the cells. In the cerebellum Purkinje cells are sometimes found partially or wholly calcified, and often their widely branching processes are covered in places by fine granular incrustations. After poliomyelitis calcification of ganglion-cells often occurs in the atrophièd anterior horns of the spinal cord and is occasionally accompanied by a more or less extensive calcification of the capillary vessels.

7. Connective tissue is the most frequent seat of calcareous deposits. The fibers undergo so-called *mineral metamorphosis;* they are loaded with rows of fine granules, which, as they grow, develop into rod-shaped, cylindric, nodular, irregular deposits. The alteration occurs most frequently after hyaline degeneration of the connective tissue, and it may be said that hyaline degeneration of connective tissue always predisposes to calcification. In large vessels, especially, the intima and the media often exhibit this calcification, after first becoming thicker, indurated, and hyaline. In the large vessels the process is one of the most frequent concomitants of atheroma, and must not be confounded with the ordinary form of calcification, which takes place almost regularly in advanced age, without being preceded or accompanied by degenerative processes (see under 1). Atheroma of the large vascular trunks is attended by proliferation of the connective tissue and by fatty changes, with the formation of cavities from the melting-down of the tissue. The thick connective tissue frequently contains large and small calcareous masses, which at first appear as isolated, minute granules; later the deposition becomes extraordinarily extensive, taking the form of jagged masses of irregular shapes, like the fragments of a broken vessel, with sharp edges; these masses rarely surround the blood-vessels, and are usually better developed on one side than on the other. In transverse section these foci of calcification *appear* in the form of irregular, jagged bands, interrupted

in many places by circular gaps. The consistence of the calcareous masses is not uniform, and the tinctorial reaction to hematoxylin is accordingly irregular and patchy (Plate 17, Fig. 2). The gaps in these ribbons correspond to the cavities left by the melting-down of the tissue; in a recent preparation they appear to be filled with friable masses of detritus, in which glistenining cholesterin plates, resembling fish scales, are visible to the naked eye. The cholesterin plates may be numerous and form enormous masses, among which may be seen fatty acid crystals in the form of margarin needles arranged in bundles, fatty granule cells, and free fat, usually in minute droplets. In a stained preparation the gaps are seen to contain only a a fine network, like connective-tissue cells that have undergone fatty degeneration, while the fat itself and the masses of cholesterin have been removed. The calcification often involves the entire width of the intima, while toward the lumen the pieces of calcium are covered by a layer of connective tissue which is practically homogeneous and sparingly supplied with elastic fibers. In advanced cases the calcification may spread in the media, without, however, altogether crowding out that layer; the adventitia, on the other hand, always escapes. Not infrequently this petrifaction extends from the arch of the aorta to the endocardium of the aortic and mitral valves, and rod-shaped, lamellar or irregular, jagged, and ridge-like deposits make their appearance and cause shortening of the valves and their adhesion to one another. In these cases also the process of calcification is preceded by a complete conversion of the connective tissue into a homogeneous mass. Not only the large vessels, but all arterial branches as well, may be attacked by atheroma and their walls may subsequently undergo calcification; in the small arteries, as, for example, the coronary arteries of the heart and the cerebral vessels, the process often leads to the formation of rigid, hard, calcareous cylinders, sometimes with simultaneous narrowing of the lumen and complete loss of elasticity. This process of induration, which follows atheroma and ultimately leads to calcification, is designated *arteriosclerosis*. In the capillaries also hyaline degeneration or hyaline thrombosis may be followed by extensive calcification.

In addition it is common enough to see calcification take place in newly formed connective tissue in various portions of the body, especially after a chronic inflammatory process. Thus, calcareous plates are likely to be deposited in pleural scars after the connective-tissue fibers have lost their nuclei and have become fused into a compact, sclerotic, hyaline mass. In these cases also the calcification often assumes enormous dimensions, and an entire lung may be imbedded in a calcareous cuirass; in chronic fibrous pericarditis the heart may be surrounded by calcareous plates and continuous rings which suggest armor-plates. A favorite seat of hyaline metamorphosis is the connective tissue of the thyroid gland, as has been stated, and accordingly secondary calcareous deposits are also found frequently in this organ; they may be so extensive that large portions of the gland contain a veritable calcareous framework or are in a large part converted into masses of lime (*struma petrificans;* calcareous goiter). Organized thrombi also frequently become calcified, and in this way are formed *arterioliths* and *phleboliths*, which in case of canalization of the thrombus often take the form of mere scaly deposits in portions of the wall; they are then readily mistaken for calcification on the basis of arteriosclerosis. It has been stated already that infarcts which have been replaced by connective tissue may become infiltrated with a friable, calcareous material, which sometimes forms more or less distinct concrements. Chalky, pulverulent, whitish masses of this kind are hard to distinguish from calcareous tubercles.

Circumscribed connective-tissue growths, with hyaline degeneration and secondary calcification, sometimes occur in the spinal pia. The process leads to the formation of linear, jagged, or scaly plates, as hard as stone, which have been erroneously designated osteomata of the pia, but in reality consist only of calcified connective tissue, *without any true* bone-formation. In fact, it may not be amiss to repeat that calcification of connective tissue is to be rigidly distinguished from true ossification, which also occurs; histologically, the point of distinction is the formation in ossification of the lamellæ with Haversian canals and true bone-corpuscles provided with processes, while petrification consists merely of coalesced calcareous granules. While, therefore, the latter process is distinctly degenerative in character, ossification implies true metaplasia, which will be discussed later in the section on Tumors. [It may be remarked here, however, that true ossification may take place in connection with various forms of pathologic calcifications—*e.g.*, calcareous tuberculous foci in the lungs.—Ed.]

Calcareous deposition occurs quite regularly around larger dead parasites—*e.g.*, in the capsules of dead trichinæ and of sterile or dead ecchinococcus cysts; the bodies of the dead parasites themselves may also undergo complete calcification.

To this group belongs also the calcification which so often is observed in the stroma of various kinds of tumors. Occasionally an entire connective-tissue tumor falls a prey to calcification; for example, chondromata, endotheliomata, fibromata, especially myomata—the latter sometimes form balls as large as a man's head, of a stony hardness, and an extraordinarily dense structure and a corresponding weight. Particularly in the brain occur tumors of the type of fibroma or endothelioma, in which calcification may form in peculiar concentric, linear, spheric, or mulberry-shaped structures—so-called *spheroliths*. This form of tumor is commonly known as *psammoma*. The term conveys no definite idea in regard to the histologic structure and mode of origin of the tumor to which it is applied; it is simply used to indicate the presence of calcareous deposits analogous in structure to the normal brain-sand in the plexuses and in the pineal body. It is almost needless to say that calcification sometimes occurs in the stroma of epithelial tumors.

8. The parenchyma of certain epithelial neoplasms has a tendency, from the very beginning or soon after their

formation, to undergo calcification—that is to say, the epithelial cells themselves or the nest-like accumulations become infiltrated with crumbling masses of calcium salts, preceded by necrosis of the cells and disappearance of the nuclei. These tumors, which are seen chiefly in the ovary, have been designated *psammocarcinomata*. Similar tumors have also been described in the mammary gland. A special form belonging to this group is the so-called *calcifying epithelioma*, which begins in the squamous epithelium of the external skin and is sometimes multiple. Collections of epithelial cells, like epithelial pearls, or more diffuse growths of squamous epithelium, present scattered calcareous foci within which the cells either present a peripheral, calcareous envelop within the body, or suffer complete conversion into calcareous matter after disappearance of the nuclei (Stieda, Chilesotti). (See Fig. V.)

9. In *fat-necrosis*, which occurs chiefly in the subperitoneal fatty tissue and in the interacinous fatty tissue of the pancreas, it is not uncommon, as Chiari first pointed out, to observe the appearance of yellowish-brown, circular and angular clumps, rings, or shapeless masses of a dull, glistening appearance, which take the place of the fat-cells; or their capsules, after the fat has disappeared, may be filled with the sheaves of needles representing crystals of calcium in combination with fatty acids. [H. G. Wells has shown that fat-necrosis may be produced experimentally by intraperitoneal injection of extract of pancreas.—Ed.]

10. So-called *calcareous metastases* (Virchow) are sometimes observed in diseases of the skeleton associated with decalcification of bone—for example, in the case of tumors which cause disintegration of bone-substance and in tuberculous caries. Either the bone salts are not completely dissolved by the pathologic process or they are secondarily precipitated at certain places from the fluid, in which they are contained in an abnormally concentrated solution; under such conditions actual deposits of calcium are found in organs like the lungs, kidneys, the gastric

mucous membrane, involving the intercellular substance as well as the parenchyma cells.

11. Calcification often develops in dead portions of tissue or in masses of inspissated secretion. In this wise concretions are formed in the excretory ducts of salivary glands and of the pancreas, consisting of desquamated epithelium, amalgamated into a solid mass by the inspissated secretion (*salivary calculi; pancreatic calculi*). In this way also calculi are formed in the lacunæ of the tonsils from the cast-off epithelial cells mixed with the stagnating secretion of the mucous membrane. In cases of contracted prepuce *preputial calculi* result from a mixture of sebaceous material and squamous epithelium derived from the smegma. The most striking example of calcification of dead tissue is afforded by the so-called *lithopedia*, which result from impregnation of the tissues of retained dead fetuses; the calcification may attain such a degree that the entire structure ultimately represents a mineral substance of a stony hardness.

12. Finally calcium appears in the organism under pathologic conditions in the form of *concretions in the urinary and in the biliary passages*. In the urinary calculi the calcium is combined with uric acid, phosphoric acid, or oxalic acid, having impregnated an albuminous ground-substance which traverses the entire calculus from the center to its periphery like a kind of framework; this albuminous substance is readily demonstrated by dissolving out the calcium from the concretion. Even the smallest concretions present a stroma of this kind—for example, the granules in the so-called uric-acid infarct of the newborn, which is regarded by Ebstein (Fig. VI.) as a pathologic product and attributed to degenerative processes in the epithelium of the convoluted tubules, which, in turn, probably depend on the injurious influence of increased uric-acid excretion.

In *gall-stones* also, which, in addition to calcium, harbor bile-pigment and large masses of cholesterin, a similar organic framework may be demonstrated. [It has been shown that in biliary calculi the nucleus may *be formed* by masses of bacteria, especially typhoid bacilli; which have been recovered from the interior of gall-stones.—ED.]

PIGMENT.

Under normal conditions the various colored bodies or pigments in the organisms occur in two forms: (1) in solution, and (2) in granular form. The first class includes hemoglobin and bile-pigment; the second class, the pigments which are responsible for the color of the skin and its appendages, the retina, and the choroid. The quantity of pigment, even in the normal state, is subject to great variations in the different races and even in different individuals of the same race. Certain internal organs also, especially the heart muscle and the suprarenal capsules, normally contain a certain quantity of granular pigment.

The pigments occurring in the body under pathologic conditions may be divided into the following groups:

1. Pigment derived from hemoglobin. (*a*) From extravasated blood. (*b*) By metamorphosis and disintegration of red blood-cells without extravasation.
2. Bile-pigment.
3. Pigments produced in the protoplasm of cells by their metabolic activity.
4. Pigment ultimately derived from the skin or from the eye.
5. Pigmentary material introduced into the body from without.

Pigment Derived from Hemoglobin. — The changes to which red blood-cells that have escaped from the vascular system through lacerations or by diapedesis are subjected have already been described in detail in the section on Hemorrhage, and I shall now refer briefly to the pigmentation which takes place in certain organs as the result of slow but protracted hemorrhage and the characteristic changes to which it gives rise. Here belongs, in the first place, the so-called *brown induration* which may be observed in many organs, especially in the lungs, after the flow of blood has been impeded for a certain length of time, as in the presence of cardiac lesions. The constant increase of pressure in the venous and capillary vessels ultimately leads to continuous small hemorrhages by diapedesis. The red blood-cells escape into the surrounding tissue and fall a prey to the pigmentary metamorphosis already described. Within the lung the granules of hemosiderin and hematoidin which result from this process are found imbedded in certain cells, some of which must be regarded as epithelial cells from the alveolar lining, others as wandering connective-tissue cells and lymphocytes. The particles of pigment are in part deposited by these cellular structures on the inner surfaces of the lung, whence they may enter the bronchi and be expelled with the bronchial secretion in the form of so-called "heart-failure cells." Others accumulate in larger and smaller masses in the connective tissue of the pulmonary stroma, which becomes thicker as the result of the congestion; some are carried into the lymphatic system and deposited in the lymph-glands, where an opportunity is afforded for the further elaboration of the pigment (Plate 18, Fig. 3). Similar processes of passive congestion, with induration, associated with pigmentation from the breaking-down of red blood-cells, sometimes take place in the liver, in the kidneys, and in the gastro-intestinal canal. Intense pigmentation from extravasated hemoglobin is produced in so-called internal and external hemorrhagic pachymeningitis (see Vol. II.). The newly formed connective-tissue membranes in that disease usually present all the stages through which the hemoglobin passes from the intact red blood-cell to the crystalline intracellular hematoidin.

The following are also to be classed among the pigmentations derived from the blood:

(*a*) *Hemosiderosis.*—This process is physiologic in the blood-forming and blood-destroying organs (the spleen, liver, and bone-marrow) and it may be increased by any process that tends to increase the destruction of red blood-cells or artificially, as, for example, in pernicious anemia

PLATE 18.

FIG. 1.—**Pigment from an Old Apoplectic Focus in the Cerebrum** (Hemat.-eosin. × 280.): 1, Spindle cells from the newly formed connective-tissue capsule; 2, newly formed blood-vessels; 3, amorphic hematoidin; 4, large nodular masses; 5, hematoidin crystals; 6, imperfectly formed, small amalgamated crystals.

FIG. 2.—**Hemosiderin from a Small Apoplectic Focus in the Cerebrum** (Carmin-potassium ferrocyanid and hydrochloric acid. × 280.): 1, Loose-meshed connective-tissue capsule of the apoplectic focus; 2, tissue diffusely infiltrated with hemosiderin; 3, larger, intracellular masses of hemosiderin.

FIG. 3.—**Pigmentation of the Lung in Brown Induration** (Hemat.-eosin. × 300.): 1, Swollen alveolar epithelium; 2, alveolar epithelium filled with blood-pigment; 3, intracellular blood-pigment within the proliferated interstitial tissue.

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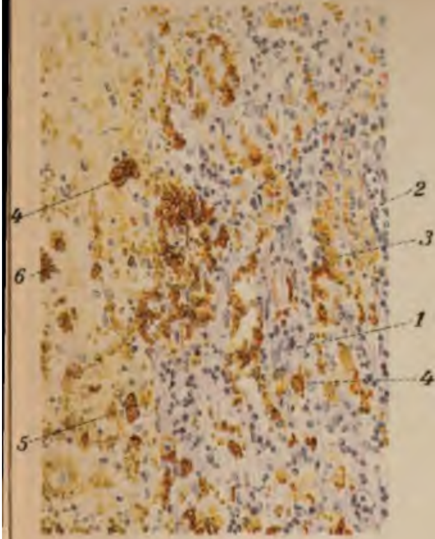
and in artificially produced plethora. In artificially produced hemolysis, as in poisoning by toluylendiamin, the hemoglobin escapes from the erythrocytes into the plasma, while leukocytes take up the red blood-cells, especially in the spleen, in the capillaries of the gastro-intestinal canal, and in the bone-marrow. From these situations cells containing red corpuscles (globuliferous) are carried to the liver, where the hemoglobin is broken up into bile-pigment devoid of iron (bilirubin), which is excreted into the bile-passages, and a ferruginous remainder, which is taken up again by leukocytes in the form of hemosiderin and by them distributed and deposited in various organs by the blood and lymph current (Biondi).

In pernicious anemia an abundant deposition of very finely granular, pale brown or yellowish pigment giving the iron reaction takes place, especially in the liver and also in the bone-marrow and in the kidney. In the liver this pigmentation is distinguished morphologically from bile-pigment by the greater minuteness of the granules (Plate 19, Fig. 1); cirrhotic livers may present pigmentation with hemosiderin (Kretz). The production of cirrhosis with pigmentation is usually attributed to a change *in the comp*osition of the blood and a simultaneous altera-

Tab.18



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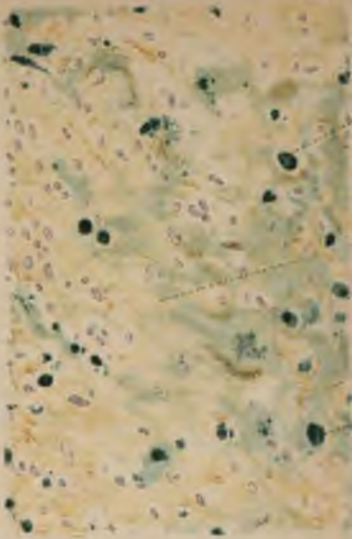

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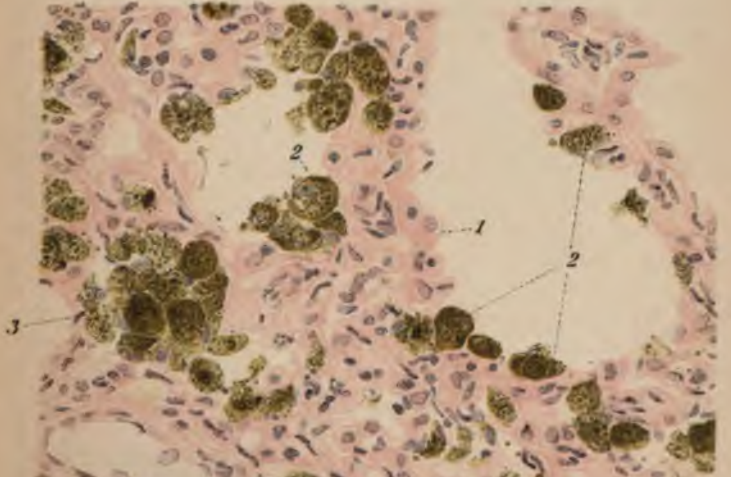


Fig.3

tion of the liver-cells. The liver-cells are unable to convert the red blood-cells into hematoidin, and pigment, deposited in the cells as hemosiderin, represents a preliminary ferruginous stage of hematoidin.

(*b*) *Hemochromatosis*, which was first described by von Recklinghausen, is also associated with the breaking-down of red blood-cells. It is often attended by extensive hemosiderosis in the liver, lymph-glands, and fatty tissue [also of the pancreas; the pancreas and the liver may show extensive cirrhotic changes—pigmentary cirrhosis, sometimes associated with diabetes.—Ed.].

The smooth muscle-fibers of the wall of the stomach and intestine, the blood- and lymph-vessels, the urinary bladder, the ureters, the vasa deferentia; the connective-tissue sheaths of blood-vessels and glands which are richly supplied with lymph-spaces; and, finally, the epithelium of the gastric and intestinal glands, the salivary and lacrimal glands, the mucous and sudoriparous glands, may show pigmentation in the form of an intracellular, finely granular, light-brown pigment, devoid of iron, which has been designated by von Recklinghausen *hemofuscin*. In the intestinal canal the pigmentation is often so intense as to give the peritoneum everywhere, or in certain places, a dark-brown appearance. The pigment is evidently derived from small capillary hemorrhages or diapedeses, and is to be regarded as the expression of a hemorrhagic diathesis. It is generally believed that the hemofuscin is brought to the tissue in solution and subsequently undergoes concentration within the cells. It has been found that the musculature of the intestine in the adult, at least in some of the cells, even under normal circumstances, almost without exception, contains minute, yellowish pigment-granules devoid of iron, and that the number of these granules increases in proportion to the individual's age. The deposition of these pigment-granules is increased by cachectic conditions, especially chronic tuberculosis and carcinosis. In severe grades of alcoholism the pigmentation is sometimes intense. As a rule, the jejunum is most severely affected, and the ileum, cecum, and colon less so.

PLATE 19.

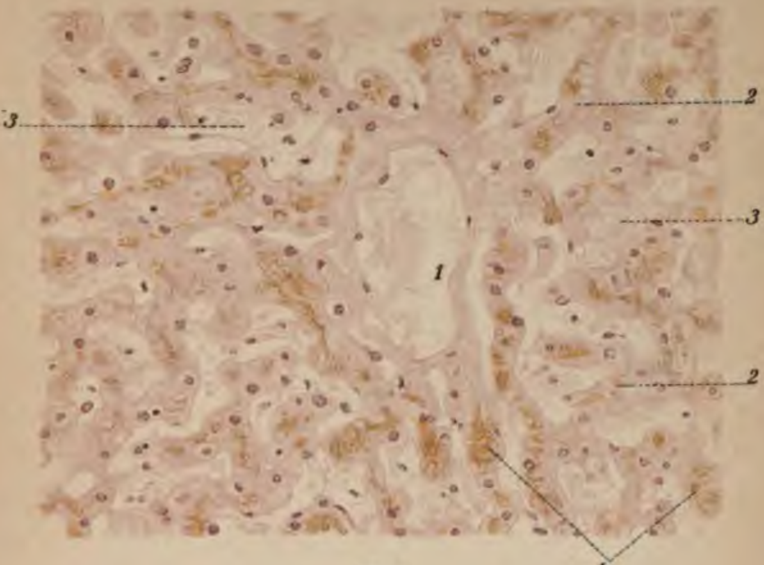
FIG. 1.—**Hemosiderosis of the Liver in Pernicious Anemia** (Hemat.-eosin. × 280.): 1, Central vein; 2, small cords of liver-cells with fat-vacuoles; 3, dilated liver capillaries; 4, finely granular hemosiderin deposited in the liver-cells.

FIG. 2.—**Pigmentation of the Brain in Chronic Malaria** (Hemat.-eosin. × 280.): 1, Brain substance; 2, small arteries with abundant deposits of melanin in their walls; 3, capillaries in transverse section.

The pigment is found everywhere, either exclusively or much more abundantly in the longitudinal, as compared with the circular, muscle-bundles. The cells themselves do not appear to be atrophic; frequently, indeed, they are enlarged and contain pigment-spindles—*i. e.*, large spindle-shaped accumulations of pigment, which is usually finely granular and almost completely obscures the nuclei (see Vol. I., Plate 55, Fig. 2).

(*c*) Under the name of *ochronosis* Virchow described a peculiar, inky black pigmentation of the cartilages, tendons, ligaments, and articular capsules, which sometimes also attacks the intima of the aorta and the lymph-glands. The discoloration is produced by a diffuse imbibition of the intercellular subtance or sometimes by the deposition of granular pigment. Virchow attributes its origin to an increase of the brown discoloration of cartilage frequently observed in old people, and believes that the pigment is derived from hemoglobin. [Concerning new cases of ochronosis and its relation to alkaptonuria, see Osler, *The Lancet*, Jan. 2, 1904.—ED.]

(*d*) Chronic malaria is accompanied by a smoky-gray discoloration of many organs, especially the liver, brain, spleen, and bone-marrow, which has been designated *melanemia*. The phenomenon is attributed to the destruction of the red blood-cells by the parasitic hemamœbæ (plasmodia) during their development, with the production of a black pigment from the hemoglobin of the destroyed cells. On microscopic examination the organs mentioned, especially the walls of the smaller arteries and capillaries,



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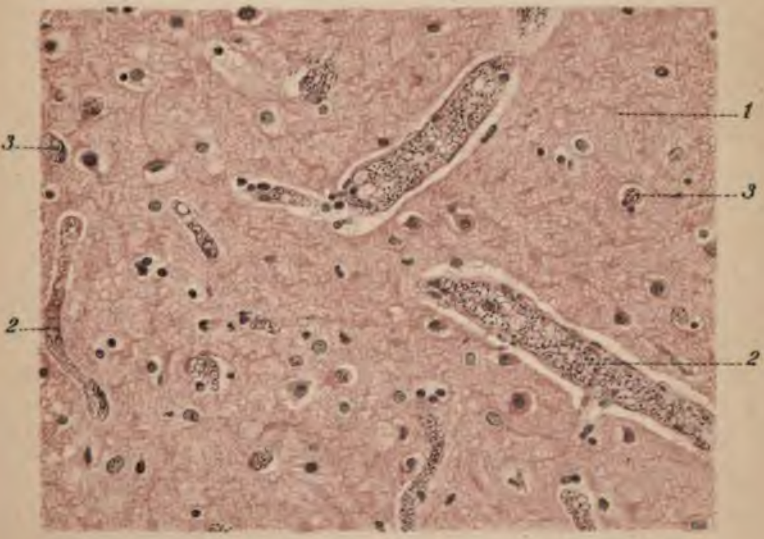

Fig.2.

Lith. Anst. F. Reichhold, Münch

are often found to contain an extraordinarily large number of fine black granules, which resemble particles of Chinese ink. These particles are in part intracellular, leukocytes especially being often completely loaded with them, and in part intercellular, replacing the cement of the endothelial cells (Plate 19, Fig. 2). The granules do not give the iron reaction.

(*e*) Finally, the pigment which lends the peculiar, intensely green color to certain sarcomatous tumors that usually originate in the periosteum is also attributed to special alterations of the hemoglobin. The peculiar greenish color, which, as a rule, is well marked only in the recent state, has given to these tumors the name of *chloroma*. As their occurrence is occasionally found associated with pernicious anemia, the discoloration has been attributed to the disintegration of red blood-cells which takes place at the same time, although the iron reaction cannot be demonstrated in the pigment.

Jaundice; Bile-pigment.—The pigmentation known as icterus or jaundice is due to bilirubin, which does not contain iron. It may arise in one of two ways: Either the hemoglobin is converted within the vascular system into bilirubin, which is identical with hematoidin, and precipitated in the organs, a condition described as *hematogenous jaundice;* or the production of bilirubin in the liver is increased and the pigment is deposited in abnormal situations—*hepatogenic jaundice.* Jaundice is usually followed by diffuse imbibition of the intercellular substance, as well as of the cells; only in very high grades of jaundice is the pigment deposited in the form of particles and granules within the cells. Hematogenous jaundice is sometimes observed in the new-born, and finds its expression in the appearance of a crystalline pigment in the form of ruby-red, rhombic plates, especially in the kidneys, a process which is also designated *bilirubin infarct.* The crystals are chiefly found within the uriniferous tubules, and may also be present in the blood, probably as a result of postmortem changes. The presence of bilirubin is demonstrated under the microscope by means

PLATE 20.

FIG. 1.—**Congestive Jaundice of the Liver in Carcinoma of the Head of the Pancreas** (Hemat.-eosin. × 280.): 1, Central vein; 2, cords of liver cells; 3, liver cells with diffuse icteric pigmentation; 4, bile-pigment cast from a small bile capillary; 5, intracellular secretion-vacuoles filled with bile-pigment.

FIG. 2.—**Pigmentation of the Skin in Addison's Disease** (Hemat.-eosin. × 280.): 1, Stratum corneum; 2, rete Malpighii; 3, intensely pigmented, cylindric basement layer; 4, chromatophores in the cutis; 5, papillary body.

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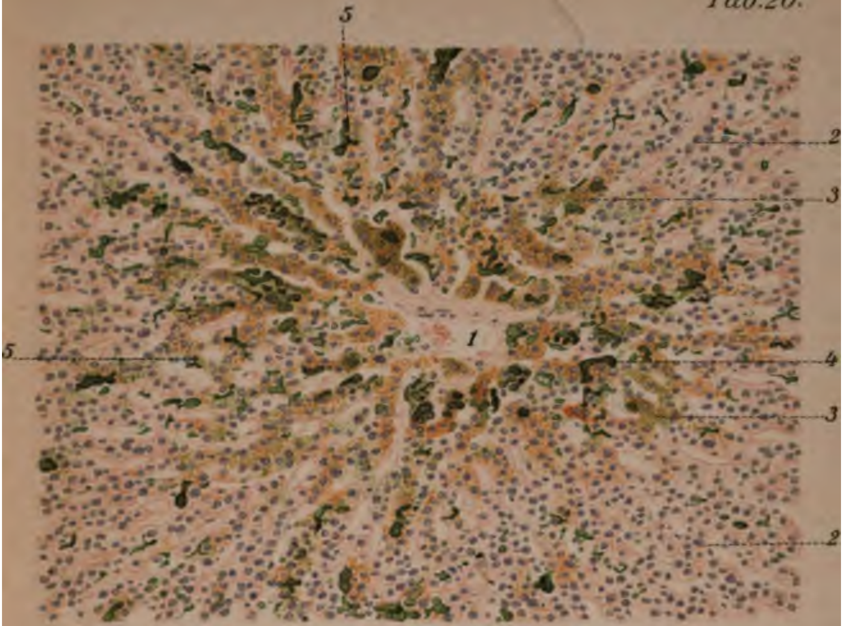
of the well-known Gmelin's reaction with nitric acid containing a little nitrous acid. The crystals present a rapid play of colors, passing from green to red and finally to yellow.

When the flow of bile from the liver is obstructed, the secretion is dammed back in the bile-ducts and the resulting *obstructive jaundice*, as it is designated, affects the most minute processes of the cells. The central portions of the liver acini are especially involved (Plate 20, Fig. 1), and are loaded with a dark, green pigment, which in part leads to diffuse imbibition of the cell and in part is deposited within the cells in the form of sausage-shaped, globular, or branching structures. Sometimes these structures may be traceable from the intercellular bile-capillaries into the so-called secretion-vacuoles of the cells. The minutest biliary passages then appear to be injected with dammed-up and inspissated bile. The endothelial cells of the blood-capillaries also may be diffusely impregnated with green pigment. The liver-cells frequently undergo fat-infiltration through the deposition of numerous small fat-granules. In severe grades of universal jaundice the icteric pigment may be deposited in other organs, also in the form of granulous or irregular masses; thus, for example, in the kidneys, where the pigmentation chiefly attacks the epithelium of the convoluted tubules, which are sometimes completely filled with a compact mass of minute bilirubin granules (Plate 80, Fig. 2, Vol. II.). In these cases the casts formed from the epithelial cells which



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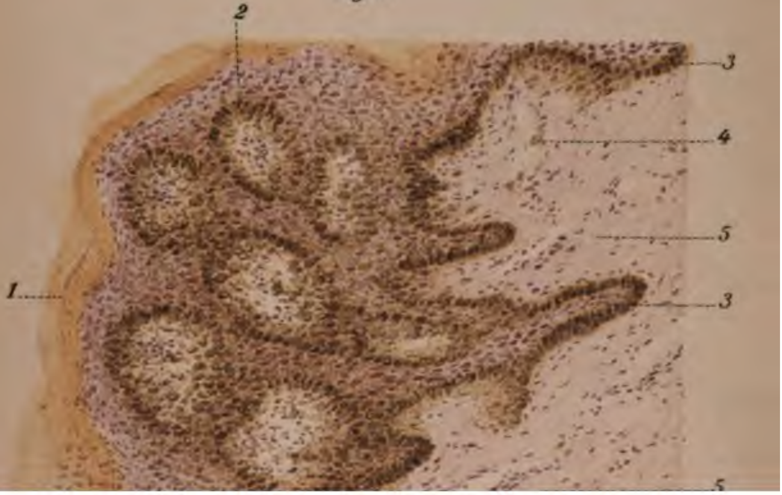

PLATE 20.

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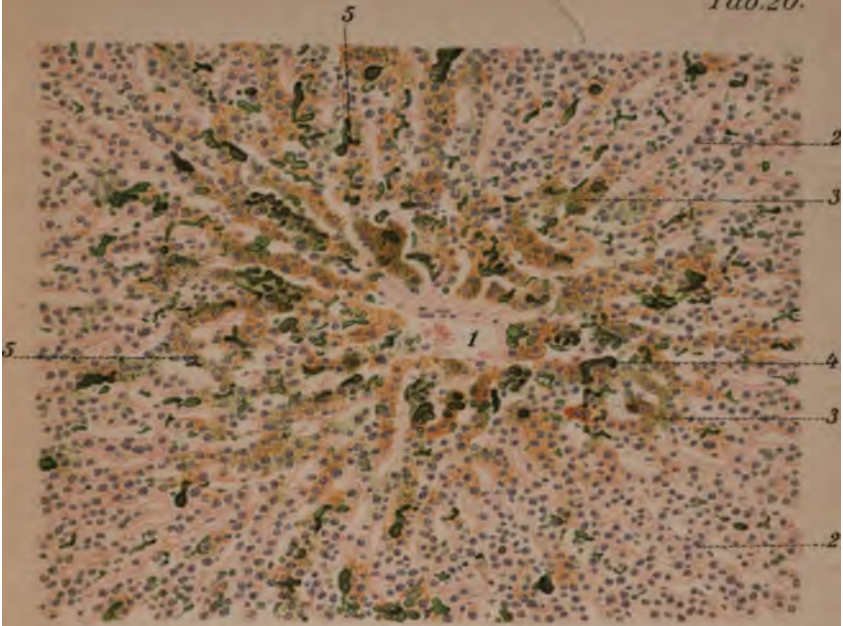

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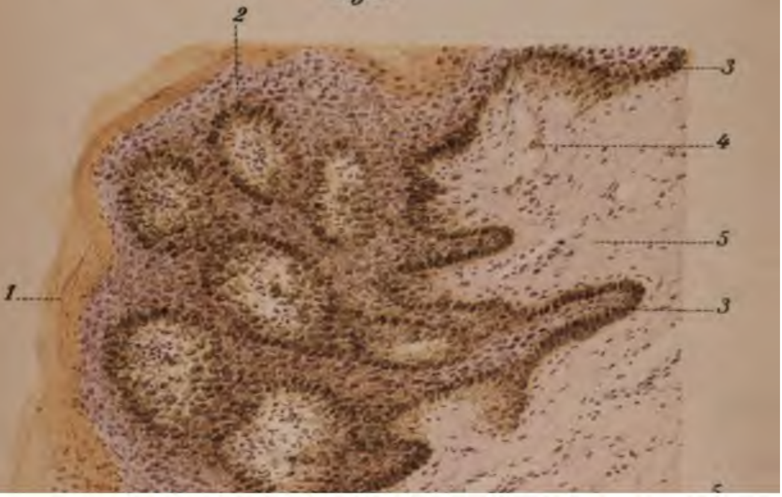


have been cast off as the result of the fatty change in the renal epithelium that takes place at the same time, as well as waxy casts consisting of an albuminous substance, or hyaline casts, also appear infiltrated with bile. The granular bile-pigment may even deposit itself in the heart muscle; the muscle-cells appear diffusely infiltrated with minute granules, thus differing from the pigmentation that is observed in brown atrophy.

3. The pigment, which is normally deposited in small quantities within the cells of the heart, kidneys, the suprarenal bodies, and testicles, is regarded as the result of **metabolic cellular activity.** The pigmentation usually increases in advanced age, when the corresponding organs also undergo atrophy (compare Atrophy). This pigment is formed within the corresponding parenchymatous cells. It is a normal product of cell-metabolism, and accumulates with old age. There is not the slightest reason for deriving this pigment from the pigments of the blood.

4. The fourth group is formed from those pigments which are normally present in the skin and in the eye, and which, under pathologic conditions, undergo an enormous increase both in the skin and especially in certain tumors which have their origin in the skin or in the eyeball. In contradistinction to the pigments derived from the blood, these pigments have been designated **autochthonous pigments,** on the ground that they are formed in the cells themselves through the metabolic activity of the cell-protoplasm, or are to be regarded as metabolic products of the cells.

The normal pigment of the skin is located chiefly in the basal layer of cylindric cells, and the darker the complexion of the individual, the higher this deposition of pigment extends in the Malpighian layer. The pigmentation consists of minute, spheric or prickly granules, found chiefly within, but to some extent also between, the the cells. In the basal layer rod-shaped conglomerations of pigment-granules are also found. The quantity of pigment varies greatly according to the race, and even in individuals of the same race it is subject to marked fluctuations. The corium also, especially in persons of very dark complexion, constantly contains a variable quantity of pigment incorporated in triangular, stellate, and widely branching cells. These cells have received the name *chromatophores,* and are to be regarded as pigment carriers. When white, non-pigmented, or very faintly pigmented skin is transplanted on a black individual (negro), numerous chromatophores at once appear in the corium and bring in other pigment, so that after a time the non-pigmented piece of skin becomes quite as dark as the skin which surrounds it. The chromatophores travel from the corium into the epithelium, deliver the pigment to the cells in that layer, and either return to the corium or undergo dissolution.

Conversely, when the dark skin of a negro is transplanted to a white individual, the transplanted piece at once loses its pigmentation, the pigment being transported back from the epidermis to the corium through the agency of the chromatophores. Within the epidermis these cells load themselves with pigment-granules, then begin their travels into the deeper layer of the cutis, and carry their pigment to the nearest lymph-nodes, where it may be either deposited or still further elaborated. These chromatophores, therefore, play a most important rôle in the development of every form of normal, as well as pathologic, pigmentation with so-called autochthonous pigment; but where they get this pigment from in the last instance, and whether it is to be regarded as a kind of excrementitious product of the organism, having its origin within the cells, or, as some things appear to indicate, is ultimately derived from the blood, are questions which have never been entirely cleared up. [According to Metchnikoff, whitening of hair is due to the removal of pigment by phagocytic cells.—Ed.]

An increase of the cutaneous pigment, sometimes attaining extraordinary dimensions, is observed, even in individuals who are not naturally of very dark complexion, in the symptom-complex known as *Addison's disease.* In almost all the cases disease of the suprarenal bodies, usually of a tuberculous nature, is demonstrable. Quite recently the theory has been advanced by Lubarsch, on the ground that the suprarenal glands possess a glycogen-producing function, that these organs possess the power to effect a peculiar modification of the albumin in the material derived from the blood and the tissue-juices, which modification normally leads to glycogen formation, but in other places may be utilized for the production of pigment. As a rule, there is an enormous overloading of the epidermis with brown pigment-granules, which are most densely packed and present the darkest color in the basal layer and are gradually lost as the upper layers are approached (Plate 20, Fig. 2). But the pigment which is normally demonstrable in the connective tissue of the corium also undergoes some increase, and sometimes typical, branching chromatophores are seen immediately below the basal layer, extending their processes in between the epithelial cells and thus unloading their pigment. Sometimes the small perivascular lymph-nodes in the skin are also pigmented in this disease, and even the regional lymph-glands may, under certain circumstances, exhibit a considerable deposition of pigment (Schmorl).

Finally, there should be included in this category the pigment which occurs in the skin in the form of circumscribed deposits, and is designated, according to its extent, *chloasma*, *freckles*, or *liver-spots* (ephelides, lentigines). When these patches are raised and associated with an increase of the cutis or epidermis, they are called pigmentary warts or nævus pigmentosus [pigmented mole.—Ed.]. The histologic structure of these growths will be discussed in detail in connection with the description of melanosarcoma. For the present it will suffice to mention that the pigment deposition in nevi takes place in the connective-tissue cells with more or less fully developed processes, which are situated beneath the frequently attenuated epidermis, where they form a reticular framework (Plate 21, Fig. 2). These cells are also to be regarded as chromatophores, or derivatives of the same, and are sometimes found in extraordinarily close array and densely packed with dark pigment. Sometimes a nævus pigmentosus is well developed in the new-born, or the growths develop later in life.

The fullest development of autochthonous pigment occurs in the pigmented, sarcomatous tumors which grow either from the skin or from the eyeball, and are designated *melanosarcoma*. Great caution must be observed, however, not to define every brown-colored tumor as melanotic; for under certain circumstances a continuous hemorrhage by diapedesis may lead to an almost diffuse pigmentation, especially in sarcomata which grow around blood-vessels. Even within a melanosarcoma part of the pigment may be due to extravasation of blood from the erosion of vessels or hemorrhagic infarction.

Primarily the melanin of a pigmented sarcoma is always intracellular, but it may be subsequently liberated by the disintegration of the cells. For some time afterward the masses of pigment maintain their original arrangement and remain in contact with one another; but later they are forced apart by the plasma stream, and this may lead to diffuse deposition of pigment in the tissue. Sometimes the intense pigmentation in portions of these tumors gives the imprsssion that the breaking-down of the cells must be due to the accumulation of pigment. This view has even been adopted by Rindfleisch, and some authors have even spoken of *pigmentary degeneration* of tumor-cells; in such cases the intercellular substance, of course, also becomes more or less pigmented. It is not uncommon to observe leukocytes and contractile cells loaded with pigment-granules, and the latter may also be carried in great numbers into the lymph-glands. The serous membranes, and especially the kidneys, may exhibit extensive pigmentation of the cells, as well as of the intercellular substance, and pigment in large quantities may make its appearance in the urine (melanuria).

Chemic examination of the pigments derived from these melanotic tumors fails to yield uniform results. *Berdez* and Nencki have described the pigment of these tumors as *phymatorhusin*, and that of the identical tumor in horses as *hippomelanin*, and have shown that it contains an extraordinarily high percentage of sulphur. It was thought that this pointed to the intracellular origin of the pigment; but, on the other hand, the theory of a hematogenous origin was upheld by M. B. Schmitt because many of the pigment-granules, at least temporarily, give the hemosiderin reaction (see p. 22). At all events, the chemic examination of the pigment of the skin, hair, and eyes, from which the pigment, of melanosarcomata is unquestionably derived, fails to yield any convincing reasons for deriving it from the hemoglobin. Pigmented tumors are frequently observed in albinoes, who are entirely devoid of other forms of pigment, and it is well known that gray horses are particularly liable to develop melanosarcoma. In man the tumor has been observed to occur while the pigment of nevi in other regions of the body was disappearing spontaneously, and the development of the tumor is sometimes accompanied by rapid bleaching of the hair. In these cases *vicarious pigmentation* has been said to occur.

5. The term **exogenous pigments** is applied to foreign bodies with coloring-matter of their own which enter the organism from without. The ports of entry are the respiratory and digestive organs and the skin, the the latter only in the case of wounds. The most important of these exogenous pigments is coal-dust in the lungs, leading to the condition known as *anthracosis*. This pigment was formerly believed to consist of a material formed within the body, more particularly within the lungs themselves, and derived from the blood (Hasse, Virchow); but in the year 1860 Traube demonstrated in the anthracotic pigment of charcoal workers the characteristic stippled cells of carbonified vegetable structures. The inhaled dust is chiefly deposited in the so-called dust-cells, consisting either of epithelium from the pulmonary alveoli or of leukocytes, and possessing a circular, angular, and polygonal shape. These dust-cells possess the property of conveying the pigmented foreign bodies into the tissue;

PLATE 21.

FIG. 1.—**Anthracosis of the Lungs; Deposition of Coal-pigment in the Perivascular Connective Tissue** (Alum cochineal. × 300.): 1, Endothelium of a blood-vessel; 2, intracellular pigment within the lymph-clefts; 3, large masses of free pigment; 4, desquamated alveolar epithelium containing particles of coal-dust.

FIG. 2.—**Nævus Pigmentosus from the Skin on the Dorsum of the Foot** (Recent teased preparation. × 260.): 1, Faintly pigmented connective-tissue cells; 2, spheric cells heavily laden with dark pigment; 3, free fat-droplets.

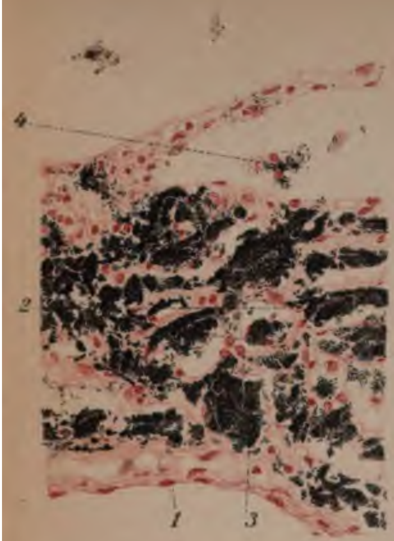
FIG. 3.—**Argyrosis of the Kidney** (**From Man**) (Carmin. × 280.): 1, Uriniferous tubules; 2, glomeruli loaded with particles of silver; 3, particles of silver deposited in the membrana propria of uriniferous tubules.

FIGURE VII.

Tattooing of the Skin of the Forearm (× 150.): 1, Corneal layer; 2, attenuated layers of rete Malpighii; 3, flattened papillæ; 4, pigment-granules within the papillæ; 5, large masses of pigment in the corium.

some of them escape from the alveoli through the cement substance between the epithelial cells, and enter the lymph-channels in the alveolar walls, to be deposited either in the various intrapulmonary lymph-nodes or to make their way into the peribronchial and peritracheal lymph-glands (Arnold). The accumulation of coal-pigment may reach an extraordinary degree in men whose occupation keeps them constantly in an atmosphere containing coal-dust (miners, stokers, chimney-sweeps). In the pulmonary tissue the black collections of dust are found chiefly in the perivascular and peribronchial connective tissue, which is densely packed with the material (Plate 21, Fig. 1). The dust is found either free or inclosed in cells, especially in the dilated lymph-clefts of the tissue; some of the pigment particles are found in desquamated cells within the alveolar spaces, and from these the greater part of the pigment is constantly eliminated by expectoration and the action of the ciliated cells of the bronchial epithelium. *When the* accumulation in the lymph-glands is excessive,

Tab. 21.



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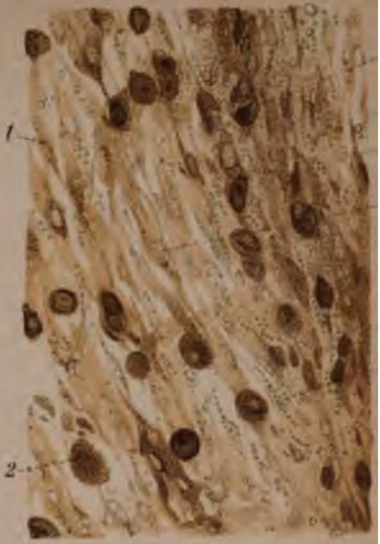

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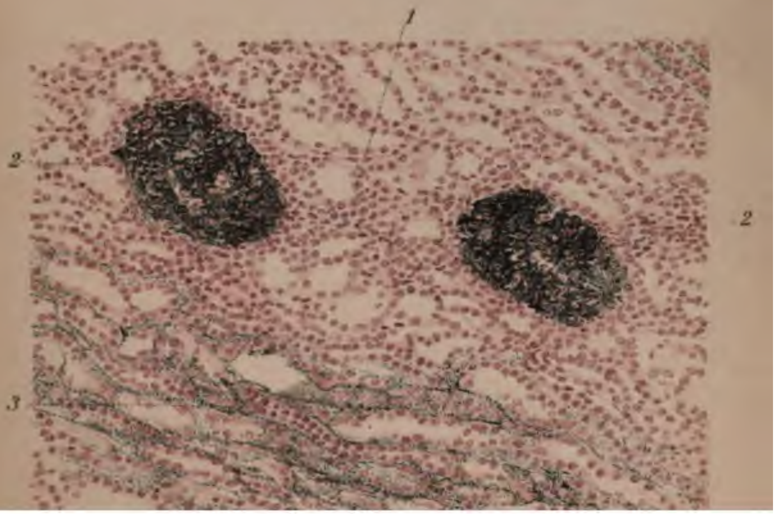

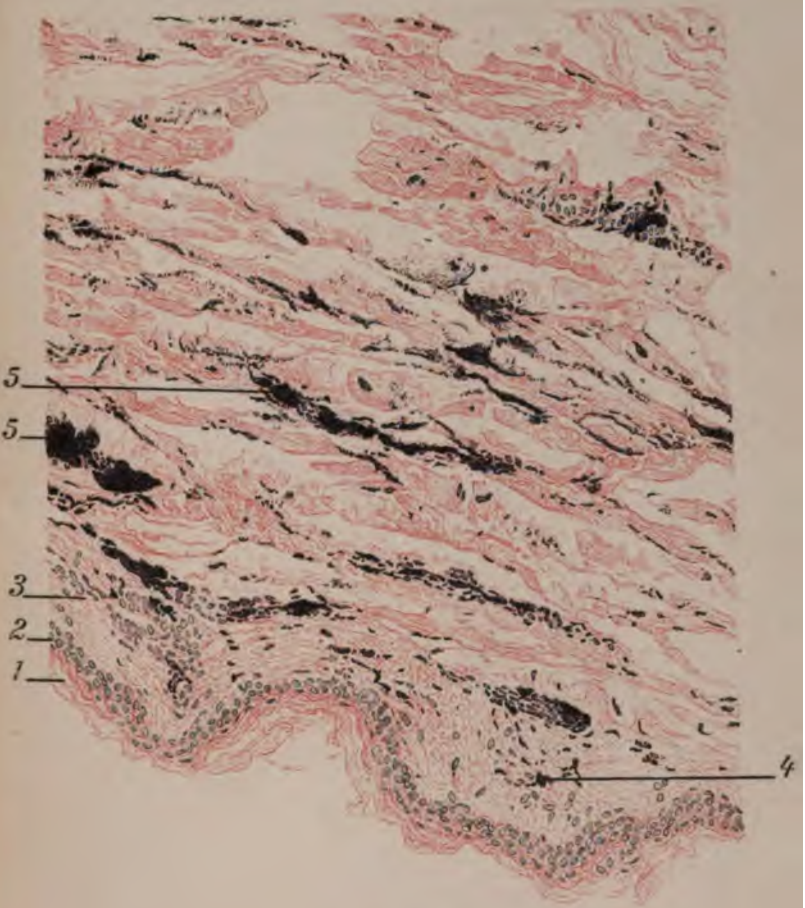

Fig. VII.

the irritation of the foreign bodies leads to chronic inflammatory processes. At first the pigment is deposited in the lymph-sinuses or at the periphery of the follicles; later a new formation of connective-tissue fibers takes place from the trabeculæ and the reticulum; and as the process continues, the gland gradually becomes much indurated and loses a large portion of its lymphatic cells. When a lymph-node has undergone these changes, it consists chiefly of sclerotic fibrous tissue densely infiltrated with free coal-particles.

Sometimes the glands enlarge and rupture into a neighboring organ—as, for instance, the bronchi; the pigment-laden glandular tissue is exfoliated, and the inky-black masses are expectorated. The enlarged glands may also cause erosion of the walls of contiguous blood-vessels, and the pigment may be carried away in the blood-stream and lead to metastasis in distant organs. In cases of pronounced anthracosis the spleen and liver are sometimes impregnated with masses of black coal-pigment. It is needless to say that other kinds of dust of different colors may produce a characteristic pigmentation of the pulmonary tissue and thus obscure its original tint. After the continued inhalation of iron oxid—as, for example, among workers in gold-leaf, paper-dyers, polishers, etc.—the lungs may appear red from the presence of the oxid (*siderosis*, von Zencker).

In the skin exogenous pigmentation is observed chiefly after the artificial introduction of coloring-matter into wounds, as in the practice of *tattooing*, which still obtains among savages, as well as among civilized peoples. The pigmented foreign bodies, consisting of coal, India ink, cinnabar, ultramarine blue, iron oxid, usually occupy the corium and the cutis, and are found either within the cells or in small lymphatic nodules, where they form masses of varying sizes (see Fig. VII.). Within the tattooed area the epidermis is attenuated, on account of the innumerable minute punctured wounds; the layers of the Malpighian layer are diminished; the papillary body is flattened, and the papillæ are poor in blood-vessels. The regional lymph-glands may be heavily laden with transported pigment-granules, which have a special tendency to form large conglomerations in the lymph-sinuses (Vol. I., Plate 14, Fig. 1).

A typical example of pigmentation of the organism with exogenous pigment derived from the gastro-intestinal canal is found in *argyria*. The drug, which is usually ingested for medicinal purposes in the form of nitrate of silver, is reduced to metallic silver in minute granules and deposited in many organs, the skin, the conjunctivæ and the sclera, the serous membranes, the dura mater, the choroid plexuses, and especially the kidney. In well-marked cases the glomeruli in the latter organs are virtually changed to silver, and on the cut surfaces appear even to the naked eye, as pitch-black granules. On microscopic examination (Plate 21, Fig. 3) the silver granules are seen in the vascular coils, and particularly in the cement substance between the endothelial cells, in unbroken rows. The nuclei of the endothelium, and even the nuclei of the epithelial cells, may be completely obscured in places by the dense accumulation of pigment. The metal is also deposited in the capillaries between the uriniferous tubules, especially in the medullary substance, and densely scattered in the membrana propria of uriniferous tubules and within the connective-tissue cells, where it collects around the nuclei. Sometimes the infiltration with silver is severe enough to produce a proliferation of connective tissue.

A somewhat similar phenomena is the so-called *blue line* in chronic lead poisoning. It is due to the precipitation of black sulphid of lead from the lead compounds circulating in the blood of the affected individual, and not, as was formerly believed, to the entrance of minute particles of lead. In this case also the deposition takes place chiefly in the endothelial cells of the blood-vessels.

NECROSIS.

Independent of the death of the entire organism and *long before it occurs*, a great variety of injurious influences may bring about the destruction of certain definite cell territories. The dead portions of tissue may retain their shape and continue to hold their former place in the organism, although their function is abolished and they cease to take part in any of the vital processes of the remainder of the body. This destruction of cellular material may take place in the following conditions:

1. In degenerative processes the course and termination of which have been minutely described in the preceding section. It was seen that under normal conditions these degenerations may take place in certain cell-complexes, causing their gradual exclusion from their original connection with the remainder of the body. Thus, for example, in the skin a constant horny change takes place in the epithelial cells of the upper layers of the rete Malpighii, with the simultaneous death of these elements and their gradual disappearance by desquamation or mechanical removal. The cornified cells suffer local tissue-death. A somewhat similar phenomenon is observed in many gland-cells; their disintegration helps to form the secretion of the gland, which ultimately appears on the surface, and the cells are thus lost to the body as building material. If this process remains incomplete and the nutrition of the cells continues inadequate for any length of time, the resulting interference with oxidation, as we have seen above, usually leads to fatty metamorphosis of the affected parts—as, for example, in certain parts after stenosis of the nutrient arteries from chronic inflammatory processes in the vessel-walls.

2. When, however, the nutrition is completely cut off, local tissue-death or necrosis of the affected parts ensues. The sensitiveness of tissues to a diminution or entire stoppage of the nutritive supply is not always the same. In the case of some perenchymatous elements, as, for example, the renal epithelium, ligation of the arteries lasting only two hours suffices to bring about the irrevocable death of the tissue, while other kinds of tissue—as, for example, skin, muscle, and tendons—are much less sensitive and withstand the effect of occlusion of their

arteries for some time. But after a certain limit has been exceeded, even the subsequent restoration of the entire blood-supply does not suffice to bring about recovery of the affected tissue; on the contrary, the flow of nutritive material appears to hasten the advent of total tissue-death and the ushering-in of processes of dissolution. The explanation of this phenomenon will be taken up later.

3. An organ or certain cell-complexes may be utterly destroyed by some overwhelming catastrophe that, nevertheless, does not endanger the life of the organism as a whole or even cause any material damage if the affected tissue is not of a very high order. Under this head belong mechanical influences—such as pressure, a blow, or a concussion—causing injury, destruction, or even the entire separation of tissue from the remainder of the body, and chemic and thermic injuries. The severest injuries of the first class are, of course, those which produce instantaneous coagulation or solution of the albuminous substances in the protoplasm of the body. The thermic causes of necrosis may be divided into burns and exposure to extreme cold; excessive heat causes tissue-death by coagulation of the albuminous substances, while protracted exposure to moderately excessive heat is usually followed by some local degenerative process. Electricity may also cause local tissue-death, especially when its action is combined with electrolytic processes in the body substances. Finally, this category includes injuries due to infectious processes that are set up by the death of circumscribed portions of tissue and by the action of the poisonous metabolic products of vegetable or animal parasites.

When death occurs suddenly in a considerable portion of a part of the body and the tissue retains its connection with the body, the process is called *necrosis;* when, however, the injurious influences enumerated lead to gradual death of individual cell-complexes, with a slow and gradual diminution of the vital processes down to the zero-point, the process is designated *necrobiosis.*

The microscopic appearance of the necrotic part varies greatly according to the cause and the special composition of the affected tissue. Typical necrosis is seen in mortification of tissue from nutritional disturbance. Such mortification most frequently occurs, as has already been stated, from embolism causing occlusion of the nutrient arteries; in animal experiments the best way to produce the phenomenon artificially is to ligate an artery that does not possess any collateral branches. After the nutritional disturbance has acted for a certain length of time, providing there has not been a subsequent inflow of blood into the infarcted region, as has been minutely described (see Embolism), the infarct, even to the naked eye, usually appears as a pyramidal mass of tissue, very pale in color, with the apex directed toward the occluded vessel; its consistence is greater than that of the surrounding tissue, and its volume, at least during the early stages, is also increased. The infarct at this period usually projects above the surface of its surroundings. Microscopic examination reveals total destruction of the cellular elements, the more minute changes in which will be described presently.

Diametrically opposite theories have existed since the earliest times in regard to the cause of local tissue-death, after the nutritive supply has been cut off. One theory, founded and advocated by Virchow and his followers, seeks the cause for the death of the cells in progressive desiccation from suspension of the blood-supply—*i. e.*, part of the tissue dies from gradual loss of its water, which is absorbed by the surrounding tissue, somewhat in the same manner as part of a plant falls off or wilts after the flow of sap has ceased.

Serious objections have, however, been raised against this theory; for in the beginning an increase in the volume of the infarcted district can be demonstrated; chemic examination does not show that there is any diminution of moisture, and, finally, it is the rule in the case of infarcts in certain tissues (central nervous system) to find that they take up water from the surrounding tissue and are thus converted into a semifluid or fluid mass. On the other hand, Weigert advanced the theory

PLATE 22.

FIG. 1.—**From the Margin of a Recent Anemic Infarct of the Kidney** (× 70.): 1, Uriniferous tubules with intact and tingible nuclei; 2, uriniferous tubules with nuclei that will not take the stain; 3, glomerulus with necrotic cells.

FIG. 2.—**Skin in Senile Gangrene** (× 280): 1, Stratum corneum; 2, rete Malpighii; the nuclei are already somewhat indistinctly seen through the tissue, and in part are barely recognizable. Some of them are vacuolated; 3, corium; the nuclei have lost the power of staining; 4, granular amorphous blood-pigment.

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that the local tissue-death is in the main due to a coagulative process in the cell-bodies and in the muscles, and he, therefore, speaks of a *coagulation necrosis.* This form of coagulation must not, however, be confounded with the formation of fibrin, which regularly takes place in infarcted districts, both within the cells, and particularly in the blood-vessels of the embolized district after stasis and secondary thrombosis in the blood-vessels have taken place. This coagulation of the cell-albumin is due to the action of the plasma-stream on the dead tissue elements, which are still capable of coagulation. The plasma-stream, both before and after the death of the tissue, enters the dead portions from the neighboring regions, even after the former have already been deprived of their own circulation. The process evidently bears a close resemblance to fibrin coagulation, although the two are not quite identical; for the dead cells furnish an abundance of ferments which enable the fibrinogen of the plasma to exert its action on the necrotic cellular material. The investigations of Schmaus and Albrecht afford absolute proof of the occurrence of this form of coagulation by the treatment of freshly isolated tissue-cells in microscopic preparation with water. When normal cells, as, for example, renal epithelia, are exposed to the action of water, a marked swelling and, later, solution of the cell-body take place—the so-called "*tropfige Entmischung.*" [This phenomenon is easily explainable as the result of absorption of water by the cells in obeyance to the laws of osmosis.—ED.] After ligation of the renal arteries

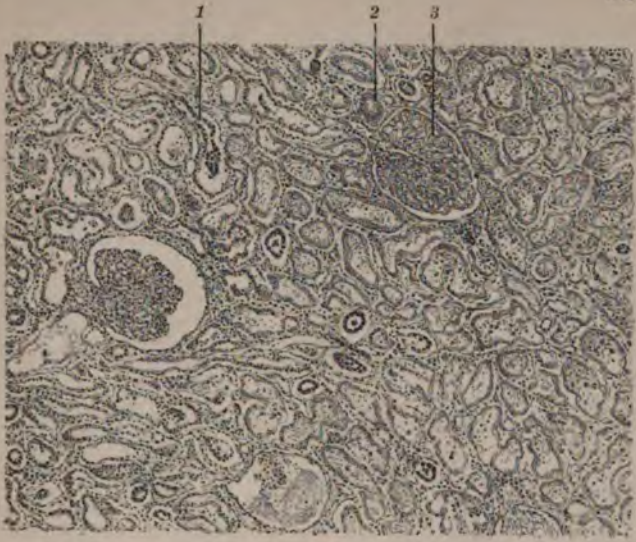
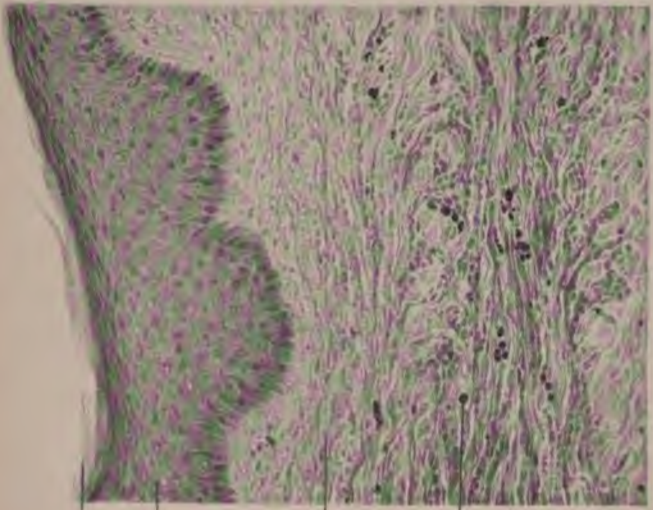


Fig. 1.



the cell-bodies in the course of a few days become granular in structure and will not dissolve in water, acetic acid, or alkalis. It is evident, therefore, that a solid body, insoluble in dilute acids, alkalis, and neutral salts, is formed from the constituents which were originally in a liquid state. It is possible that these coagulative processes may furnish an explanation for the fact that hyaline changes and calcification sometimes take place as secondary phenomena in tissues the seat of coagulation necrosis.

In addition to these chemic [and physical.—Ed.] changes in the protoplasm certain important morphologic alterations take place in necrotic tissue or tissue that is approaching the stage of necrosis; the nuclei ultimately disappear, and cell-body and nucleus are converted into a homogeneous mass. Some of these processes are extremely complicated and present numerous points of resemblance, on the one hand, to the proliferative conditions of the cell-nuclei in mitotic division of the cells, and, on the other hand, to postmortem changes produced by the processes that take place after death of the entire organisms. It is needless to say that in the latter case the picture of simple necrosis, under natural conditions, is soon obscured by the occurrence of putrefaction processes which are due to the vital activity of bacteria, but in recent sections of tissue, removed from the body with aseptic precautions and preserved in sterile receptacles, many of the processes presently to be described may be observed. These processes may be divided into various parallel groups of disintegrative changes ("Deconstitutions-processe"), any one of which may predominate over the rest, depending on the nature of the affected organ and the attendant external circumstances. One of the chief phenomena in dying tissue is a progressive disappearance of the chromatin substance of the nuclei, a process which is designated *karyolysis* (Klebs). In sections cut from such necrotic tissue the nuclei fail to take the normal, well-marked stain, as in the surrounding healthy tissue, and if demonstrable at all, they appear exceedingly pale; sometimes the cell-protoplasm also stains feebly with

PLATE 23.

FIG. 1.—**Karyorrhexis in a Recent Anemic Infarct of the Kidney** (Carmin-picric acid. × 850.): 1, Uriniferous tubules in which the epithelium is split up and fragmented and the nuclei are scarcely recognizable; 2, advanced karyolysis in the epithelium of uriniferous tubules; 3, interstitial tissue infiltrated with leukocytes; 4, hyperchromatosis of the nuclear wall and other karyorrhetic figures in the cells of the interstitial tissue and of the leukocytes.

FIG. 2.—**Beginning Cheesy Degeneration in Tuberculous Pneumonia** (Carmin; Weigert's fibrin stain. × 625.): 1, Alveolar wall; 2, swollen and cast-off epithelial cells; 3, remains of nuclei in epithelial cells; 4, surviving fibrin; 5, cheesy mass derived from disintegrated cells of the exudate; 6, hyperchromatoses of nuclear membranes.

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reagents which under normal circumstances specifically affect the nuclei. These processes, as well as the occurrence of coagulation, are attributed to the action of the plasma, it being supposed that the constant bathing of the dead portions with lymph leads to maceration and gradual solution of the chromatin. It is also quite conceivable that a preliminary loosening of the chromatin substance may take place from its natural support, the nuclear framework, the nucleoli, and the nuclear wall, so that the continued action of the plasma-stream suffices to wash them away. Synchronously, or sometimes even before, the chromatin undergoes a peculiar change of position which eventually leads to the breaking-down of the chromatin framework and its conversion into minute particles. These particles are not, however, formed haphazard and scattered about without regular order; on the contrary, the process, which is designated *karyorrhexis* (Klebs), goes through certain definite stages and appears to obey definite laws, the successive pictures suggesting a certain analogy to normal karyokinesis. Sometimes the chromatin accumulates and gives the impression that the chromatic substance is increased; thick, shapeless, biscuit- and dumb-bell shaped, or irregular, granular, and stellate particles of chromatin granules, deposit themselves on the *nuclear framework* and lead to the condition known as

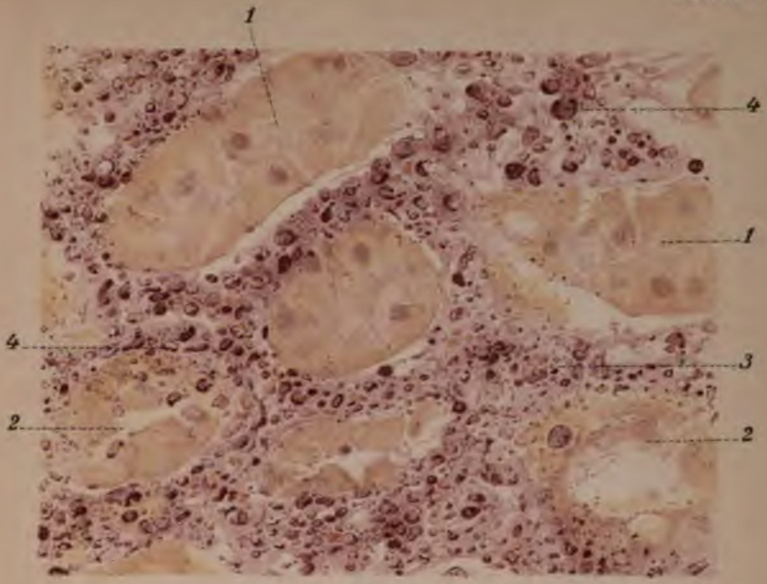
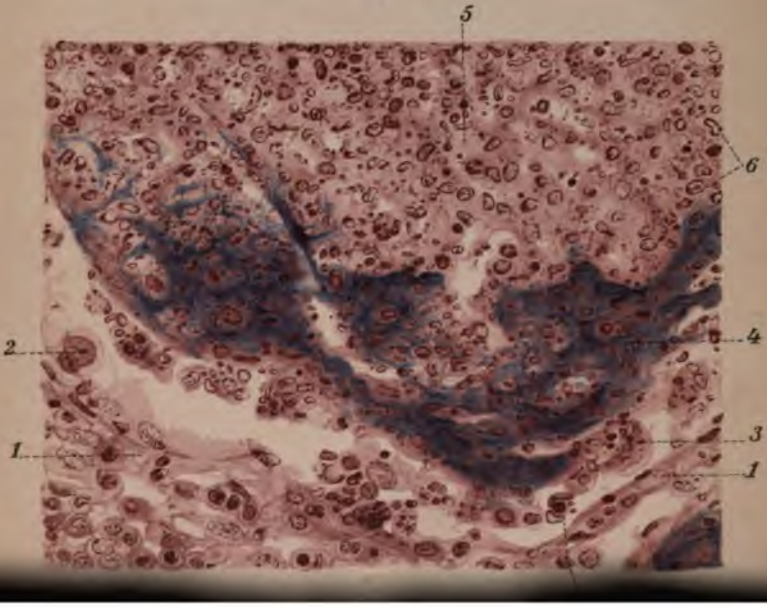


Fig.1.



hyperchromatosis of the framework. Sometimes peculiar roset-shaped figures are formed, reminding one of the daughter stars in mitosis. The chromatin particles may be arranged, either in a multiplicity of extraordinarily minute, or in a few larger groups of spheric or angular granules in the nuclear wall, in which case we speak of *hyperchromatosis of the nuclear wall.* Later the nuclear wall suffers numerous solutions of continuity, and the chromatin portions gradually escape into the cell-body in the form of budding masses. The chromatic substance either escapes from the nucleus in the form of a few large, shapeless drops and invades the protoplasm, or it may escape through the nuclear wall in the shape of innumerable minute spheres and encircle the nucleus, which has now become poor in chromatin, with budding figures resembling a mulberry or even a bunch of grapes. Finally, the wall melts completely, the nucleus ceases to represent a closed vesicle, but instead consists of a variable mass of more or less coherent fragments, arranged in the most irregular manner, and connected with one another by numerous fibrillar bridges. This stage again may lead to the production of figures which at the first glance exhibit an extraordinary resemblance to mitosis. It is to be noted in this connection that practically the same processes actually may take place in nuclei engaged in karyokinesis, only the forms are now, of course, more variegated. Not infrequently the nuclear substance undergoes inspissation, and the chromatin, which at the same time may be in a process of solution, breaks up into a few somewhat more fluid droplets. This condition, in which both the framework and the wall of the nucleus cease to be visible is designated *pyknosis* (Schmaus and Albrecht). The remaining achromatic nuclear substance also exhibits some structural changes and can no longer be distinguished from protoplasm, nor will the addition of acetic acid in the unstained condition render the nucleus visible in the cell. At this stage the disappearance of the nucleus is complete.

Up to a certain point the phenomena of karyorrhexis

PLATE 24.

FIG. 1.—**Necrotic Enteritis in Uremia** (Carmin. × 40.): 1, Completely necrotic mucosa of the large intestine; 2, the basal extremities of Lieberkühn's gland; 3, dense accumulation of leukocytes beneath the necrotic zone.

FIG. 2.—**Blister from a Burn on a Cat's Paw Three Days after the Application of Hot Sealing-wax** (Hemat.-eosin. × 66.): 1, Stratum corneum; 2, surviving rete Malpighii; 3, necrotic zone of epidermis; 4, lumen of the blister, which had been filled with serous exudate and cellular débris; 5, accumulation of leukocytes; 6, epithelium, in part newly formed, pushing its way in under the blister; 7, corium.

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may be studied in recently removed pieces of tissue, if they have been preserved with aseptic precautions, but the changes are not usually so pronounced.

The changes described as *sclerosis,* which take place in nuclei of ganglion-cells in the central nervous system after poisoning with bromin, cocain, and nicotin, are probably to be regarded as analogous to pyknosis.

Hand in hand with these changes in the arrangement of the chromatin, changes take place also in the elementary portions of the parenchymatous cells, the oft-mentioned *Altmann's granules.* At first these granules accumulate at the free border of the cells, their arrangement in rows or rods is broken, enlargement of the individual granules often follows, and finally some of the granules may be extruded from the cell-body; the last step is probably to be regarded as the effect of the washing-away of the cell by the plasma-stream after its entire framework has been loosened.

After all these phenomena of coagulation, chromatorrhexis, and chromatolysis have been completed, there finally remains a mass that is absolutely resistant to nuclear stains and only faintly tingible with anilin dyes. In such a mass, as, for example, in a completely necrotic, anemic infarct of the kidney, the structure may still be, on the whole, distinguishable, but the boundaries between the individual cells are completely obliterated (Plate 22, *Figs.* 1 and 2).

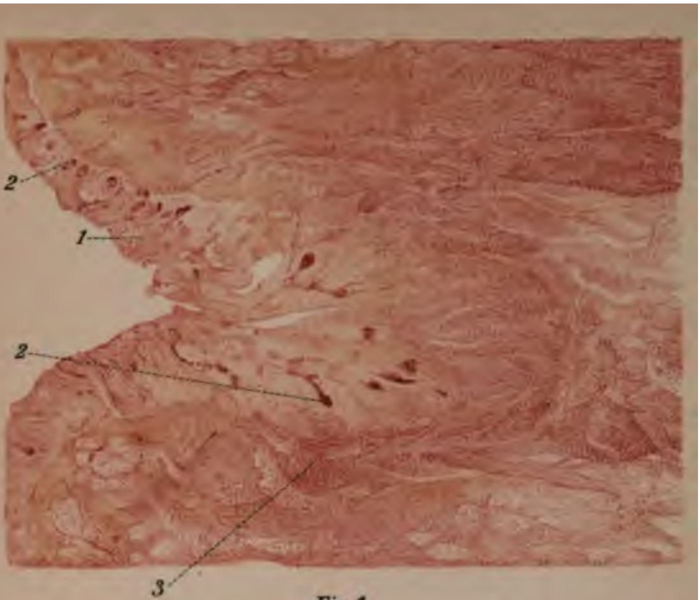

Fig.1

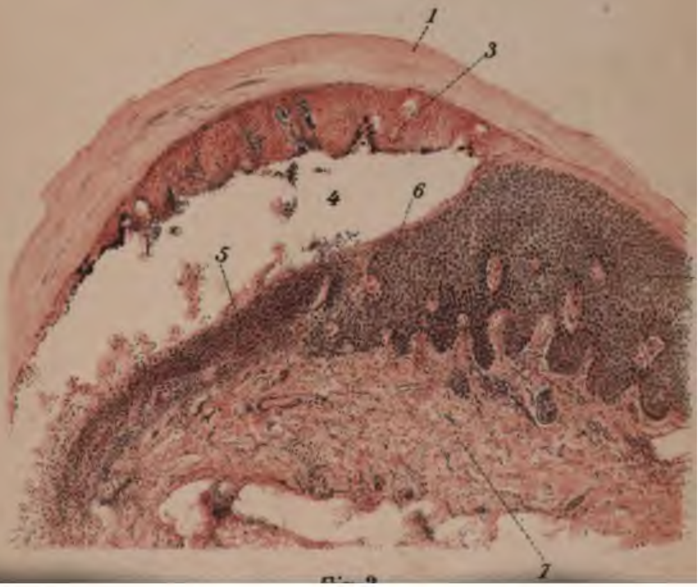

Fig.2

It has been frequently remarked that a process of *liquefaction* takes place in certain organs, as the result of the action of certain noxious agents in the dying tissue. This, for example, is always the case in the substance of the central nervous system after embolism of an artery supplying a certain region. The medullary substance evidently takes up an increased quantity of fluid from the surrounding tissue, and instead of firm coagulation taking place, the infarcted portion undergoes a colliquative change —in a word, encephalomalacia, or, in the spinal cord, myelomalacia, ensues.

The nuclei undergo the same processes of rearrangement and solution of the chromatin (karyorrhexis and karyolysis) as in the case of solid infarcts; but the cell-bodies and the medullary substance rapidly break up into exceedingly fine fat-droplets and granular detritus, which are taken up by granule-cells and carried into the perivascular lymph-spaces, where they are ultimately absorbed.

When the occurrence of necrosis is accompanied by the formation of abundant fluid exudate from the blood, as, for example, in wounds or burns of the skin, the typical phenomena of necrosis are attended by a partial liquefaction of the dead tissue. Thus, for example, the turbid contents of a blister consist largely of swollen cells of the rete Malpighii that have lost their nuclei by karyolysis and are in process of solution (Plate 24, Fig. 2). In the central layers a copious accumulation of fluid may take place, to which the characteristic appearance of the blister is due. The cellular material in the upper and lower layers continues to undergo simple necrosis.

A special form of necrosis, although not representing a fundamentally different change, is found in *caseation.* The ultimate product of this change is opaque, and is usually compared either to solid or semisolid (cream-) cheese. This metamorphosis is observed chiefly in tuberculous and syphilitic granulomata, and is evidently the result of the action on the tissue of specific poisons elaborated by the infectious micro-organisms. It is, however, not characteristic of tuberculosis or syphilis, for it sometimes also occurs in the same form in ill-nourished portions of rapidly growing tumors and in masses of inflammatory exudate that are undergoing inspissation. What characterizes caseation and distinguishes it from simple necrosis is that the death of the cells is accompanied by the collection, in the intercellular-spaces, of a mass of transudate ultimately derived from the blood, which later undergoes coagulation. Owing to its morphologic similarity to so-called canalized fibrin,—*i. e.*, a hyaline formation,—the substance has also been designated *fibrinoid* (Schmaus and Albrecht). It is probable that the dying cells take part in the formation of this substance, and in doing so lose their identity. Cheesy tuberculous tissues present all the rearrangement phenomena of chromatin which have just been described under the terms karyorrhexis and pyknosis (Plate 23, Fig. 2).

IV.—REPARATIVE PROCESSES.

HEALING OF WOUNDS AND ORGANIZATION; REGENERATION.

So long as life endures regeneration processes constantly take place in the human body; numbers of cells are used up in the performance of their functions, cast off, and lost, and these losses must be made up by the formation of new cellular elements to take the places of the old. Thus the lymphatic organs, particularly the spleen and the lymph-glands, exhibit an uninterrupted, tireless activity; their germ-centers constantly produce large numbers of young lymphocytes, which advance into the peripheral layers and thence make their way into the lymph-sinuses, to be carried along into the circulating lymph. In like manner the cellular elements of the blood, which are constantly used up by the vital processes, must as constantly be renewed, and this function during postfetal life is performed by the spleen and the bone-marrow [and hemolymph glands.—Ed.] In the skin and in all the mucous membranes the superficial cells are constantly being cast off, either mechanically, as the result of wear and tear, or by being converted into the secretions of the glands of the skin and of the mucous membranes; and in these structures also the loss must be made good by the proliferation of the cells in the adjoining layers—*i.e.*, in those situated immediately beneath. New building-stones move up to take the places of those that have been used up. Almost everywhere in the body a continuous process of minute repair is necessary, and once the material for this repair is used up, the corresponding organ suffers more or less injury which in general is regarded as a sign of age and senile atrophy.

These reparative processes, however, are rendered necessary not only by normal vital processes, but sometimes also by the sudden death or injury of large cell-complexes in the body. Local tissue injuries may take place as the result of mechanical, chemic, or thermic influences, or from a great variety of morbid processes, without permanent abolition or impairment of the function of the respective organ necessarily taking place, as all the tissues of the body possess in a variable measure the faculty of restoring parts that have been destroyed.

In the simplest cases mechanical injury leads to the production of a wound in which normally coherent cell territories present gaps and the separated portions undergo a variable degree of displacement. The tissue may be damaged by the mere fact of the occurrence of a wound; cells which, under normal conditions, are guarded against the action of the atmospheric air by a protective covering, are suddenly exposed to its influences, and for this reason alone certain consequences in the form of cellular death make themselves felt. If, for example, the superficial layers of epithelium on the external skin or on the cornea are removed, the exposed cells of the rete Malpighii die; but the defect thus produced is rapidly made good by an increased production of cells in the underlying layers; these cells are gradually pushed to the surface, are converted into horny cells, and thus the protective covering is restored. In this case, therefore, a *restitutio ad integrum* takes place, the loss is rapidly made good by cells which are identical in character with the cells that have been destroyed, and complete repair of all the destroyed parts results. This faculty of complete regeneration is not possessed by all the tissues of the body in an equal degree and also varies greatly in different species. Thus we know, for example, that amphibious animals, especially in the early stages of their life-history, possess the faculty of complete regeneration, not only as regards complex organs, but even of entire parts of the body. A divided extremity is so perfectly replaced by a new growth that the substituted portion can scarcely be distinguished from the original part. In mammals and in man this power of regeneration is less perfectly developed, but in these orders the different kinds of tissue, or rather the various differentiations of the tissues, possess in a very variable degree the faculty of replacing lost portions by others exactly like them. In some tissues this power is well developed, so that even after considerable loss of substance complete recovery in the sense of *restitutio ad integrum*, both anatomically and functionally, takes place. In other tissues, however, while the divided portions may be reunited or the loss of substance may be in part or wholly replaced, the original *status quo ante* is not attained either anatomically or functionally; for the newly formed tissue remains permanently a tissue of lower order, different from the type of the destroyed tissue, forming the so-called reparative or *scar-tissue.*

In the simplest cases healing takes place by direct union of the divided parts. But even in this case a few cells are regularly destroyed by the action of the causal traumatism; with the exception of this trifling loss, however, the tissues grow together and into one another directly, and the original continuity is restored. Very much more frequently, however, the healing of divided tissue or the restoration of gaps in the tissue takes place by regeneration—that is to say, by the new formation of extensive cell-complexes. It will presently be shown how these processes in many respects resemble inflammatory processes, the new tissue at first representing an indifferent, embryonal connective tissue—so-called *granulation-tissue.* When the normal processes of healing are disturbed by the action of mechanical causes, as, for example, contusion, thermic, or chemic agents, or particularly by the invasion of microparasites, the so-called agents of infection, the granulation tissue by which regeneration is effected at once presents a predominance of certain kinds of cells. Appearances are produced which are interpreted as inflammatory processes; these may exhibit a great many gradations which cannot be sharply separated one from the other. If, for example, the emigration of leukocytes greatly predominates over other changes, we speak of a purulent inflammation. Even in such case complete healing may take place, a form of repair which was formerly designated healing by second intention; but from the pathologic and anatomic standpoint this is not a pure "healing process," since it is marred by the presence of inflammatory processes.

A practical classification suggested by Marchand recognizes two forms of healing of wounds: (1) Primary, or direct healing; simple regeneration of epithelium after solutions of continuity; true union of wounds without loss of substance; and healing under a scab. (2) Secondary healing or indirect healing, embracing every variety of repair by wounds, by indirect means, accompanied by extensive loss of substance, and necessitating a tedious formation of new tissue.

Every reparative process in a vascular part is ushered in by certain changes which, as a rule, we include among the inflammatory processes. At first a peripheral arrangement of the leukocytes takes place, their onward movement in the peripheral zone of the blood-stream within the vessel at uniform distance from one another is interrupted, and they accumulate in the dilated capillaries and veins (Plate 31, Fig. 1). The red blood-cells collect to form dense masses, and their outlines become indistinct; a so-called *globular stasis* takes place. Owing to the abnormal permeability of the vessel-walls an increased quantity of serous fluid escapes from the vessels into the surrounding tissue, and under certain circumstances may lead to ballooning of the integumentary cells. Later the extravasated, plasma-like fluid may accumulate, fibrin may be precipitated, and these events may be attended by the same phenomena and thus produce the same changes that have just been described at length in connection with hemorrhage and thrombosis. The greater the quantity of cellular material that has been destroyed by the traumatism, the greater the quantity of fibrin ferment that is liberated, and the more fibrin is precipitated from the fibrinogen of the serous fluid. The fibrin fills out the defect and projects on the free surface of the injured tissue; if the infiltrated tissue dies in part or as a whole, the fibrin may be so intimately mixed with the tissue that it is impossible to distinguish the two sharply from each other. The fibrin not only temporarily fills the defect, such as, for example, the interval between two gaping wound-edges, but also brings about agglutination between them. At the same time the wound-surface is temporarily shut off from injurious external influences, especially that of the atmospheric air. The fibrin, however, is never more than a temporary formation; the closure of the wound by fibrin cannot be permanent, for the fibrin itself is removed later on and its mission is solely to form a bridge or point the way, as it were, for the newly forming granulation tissue, which presently takes its place and for which it probably also becomes important as nutritive material; part of it is absorbed by phagocytosis on the part of the newly formed tissue elements, the leukocytes, and the connective-tissue cells.

The inflammatory exudate which is formed during regenerative processes is never purely fibrinous, however, for it always contains a variable number of exudative cells.

The term *exudative cells* is applied particularly to leukocytes—*i.e.*, those colorless blood-corpuscles which are usually supplied with several—two, three, or four—nuclei, frequently connected by fibrillary bridges or so-called fragmented nuclei—*i.e.*, horseshoe-shaped, clover-leaf-shaped, biscuit-shaped, or sausage-shaped nuclei (Plate 30, Fig. 1).

These cells, also known collectively as polynuclear leukocytes, are allowed to pass through the intact vessel-wall by a gap of the cement substance between the cells that form the blood-vessel wall, as has been described in connection with the diapedesis of red blood-cells. The escape of leukocytes, however, represents an active process; they are provided with an ameboid movement of their own, and may assume a great variety of forms, whereas the red blood-cells, as we have seen above, are simply forced through the vessel-walls passively by the increased pressure. During their wanderings through the tissues leukocytes often assume most bizarre forms. The protoplasm sends out long, straight processes, and the nuclei follow all the extensions of the cell-body; in stained preparations the shapes of the leukocytes are often very useful to enable one to recognize other cells which may be very difficult to identify. The nuclei may send out fibrillar processes with enlarged, club-shaped extremities, or radiating outrunners, and sometimes even curious interlacing and sprouting figures (gemminations), causing the greatest possible variety in the morphology of the nucleus (Plate 31, Fig. 2). A nucleated portion of the cell may be snared off and separate, especially during the passage of the cell through narrow tissue-clefts and spaces, and thus produce direct cell-division, for the resulting parts are capable of independent life and of subsequently enlarging by assimilating nutritive material. As a rule, however, the multiplication of leukocytes in inflammatory or regenerative inflammatory processes does not take place at the seat of the inflammation, but in the blood, and as under normal conditions the proportion of leukocytes to red blood-cells is as 1 to 500, the increased demand is filled within the normal breeding-places of leukocytes—*i.e.*, the lymph-follicles. The latter send out white blood-corpuscles into the blood-stream in greatly increased quantities, so that in some cases a considerable leukocytosis takes place. The number of leukocytes that usually collect at the seat of inflammation depends on the intensity of the chemotactic action; that is to say, the disintegration of body-cells, and more particularly the presence of chemic substances, especially metabolic products of the living causes of inflammation, have an attraction for white blood-cells, the strength of which is, broadly speaking, proportionate to the intensity of the inflammatory irritation.

Inflammation is followed by the formation of new tissue; or, rather, the two processes coincide both as to space and as to time; for the reparative process is begun while the phenomena of inflammation—*i.e.*, the exudative and cellular processes which originate in the vascular apparatus, are still in full swing. In quite simple and uncomplicated cases the formation of new tissue results in complete restoration of the destroyed parts; cellular building-stones precisely similar to those that have been destroyed are formed—a regeneration of the specific organic tissue takes place. But in order that this may occur, the formation of new cells must be originated and kept up by the corresponding cells in the surrounding tissue until the defect is made good. The universal law is that new formation begins always and exclusively in tissue of the same kind. It will be seen later that within the group of the connective tissues a mutual substitution of one kind of cells for another, or a merging of one into another, may take place—*i.e.*, connective tissue may be formed from endothelial cells, and cartilage or bone from connective-tissue cells; but connective tissue, for example, is never capable of producing epithelial tissue, or vice versâ. In this sense the law first formulated by Bard, "*Omnis cellula e cellula ejusdem generis*," is universally applicable.

In many cases the proliferative faculty of all the tissues of the entire organ is inadequate to the task of making good the defect; but even in that case the gap in the tissue is bridged over, the cellular material for the purpose being supplied by the supporting structure of the corresponding tissue. A proliferation of embryonal connective tissue takes place, which is frequently designated an inflammatory new formation, because tissue in every respect identical very frequently makes its appearance immediately after inflammations. Usually the newly formed tissue is called *granulation-tissue*, because the so-called plugs of flesh, or warts, or granulations, which form on the floor of wounds also consist in the main of embryonal connective-tissue cells and blood-vessels, and this name has accordingly been applied to every other kind of new formation in which similar material is utilized, not only for the closure of wounds and the filling-in of defects, but also to replace useless tissue or parts of tissue.

It is thus seen that there is no fundamental difference between simple, direct regeneration and so-called inflam-

PLATE 25.

The Healing of Wounds.—Incised wound in the tongue of a rabbit four days old (stained with Heidenhain's iron—hemat.-eosin. × 280.): 1, Newly forming epithelium; 1′, mitosis in the nuclei of epithelial cells; 1″, direct division of nuclei in epithelial cells; 2, fibrin; 2′, fibrin deposited beneath the epithelium; 2″, remains of a lump of fibrin in newly formed granulation-tissue; 3, embryonal connective-tissue cells (fibroblasts); 3′, mitotic figures in fibroblasts; 3″, mitotic figures in asymmetric sections; 4, leukocytes; 4′, leukocyte that has penetrated into a muscle vacuole; 5, small blood-vessel with proliferated endothelium; 6, newly formed embryonal blood-vessels; 6′, mitosis in endothelial cells; 6″, vascular sprouts filled with erythrocytes; 7, remains of transversely striated muscle tissue; 7′, necrotic section of muscle; 8, bacteria deposited on the outer surface.

matory regeneration, since the latter also consists in the formation of new tissue, which, however, is always of the same kind, namely, vascular connective tissue.

After these general remarks about regeneration and the new formation of the individual kinds of tissue, let us turn, first, to the question of **regeneration of connective tissue,** because it is by far the most frequent in the body. It takes place not only as a regenerative proliferation to replace connective tissue that has been destroyed, but, as has been said, it replaces defects in tissues and organs which do not possess the faculty of reproducing their own specific cellular elements; it occurs also as a secondary process after a number of inflammatory conditions on the surface of serous membranes, for instance, and in the interior of organs; finally, it enters into all the processes of organization, in which tissue that has in some way become useless or destroyed is replaced. This process of organization we have seen repeatedly in connection with the metamorphosis of thrombi and infarcts, the "healing" of hematomata and abscesses, and, in short, whenever it becomes necessary to fill a gap in an organ.

The first changes observed in proliferating connective tissue consist in an enlargement of the individual cells and their nuclei. In place of the small, narrow spindle

Tab.25.

cells almost completely filled with the dark nucleus, larger, shorter, and thicker forms, or sometimes polyhedral protoplasmic bodies with large, pale, vesicular nuclei, and provided with several processes, make their appearance; the nuclei usually contain several nucleoli and a delicate framework of chromatin; sometimes these cells contain mitotic figures; sometimes two or three nuclei can be demonstrated in the cell-body (Plate 30, Fig. 4; Plate 25, 3). These proliferating embryonal connective-tissue cells, which represent a stage that is observable in the fetal organism, are called, after Neumann and Ziegler, *fibroblasts*.

The fibrous intercellular substance progressively disappears as the cellular proliferation continues. The cells often overlie one another and may exhibit the so-called "epithelioid" arrangement—that is to say, they may overlap one another like integumentary cells; but the comparison applies solely to the arrangement, and not to the morphology, of the cell. If the purpose of proliferation is solely to bridge over or close a defect in the connective tissue, the cells, so soon as the defect has been made good, again throw out a fibrous stroma and gradually undergo a retrogression to the well-known fixed connective-tissue corpuscles, the processes of the fibroblasts breaking up into minute fibrils at first presenting a brush-like arrangement, the cell-bodies also breaking up into bundles of fibrils arranged longitudinally in regular, parallel rows. The fibers are, therefore, derived from the protoplasmic bodies and their processes, and not from the intercellular substance, since the latter disappears entirely during the proliferative processes and during the production of the protoplasmic fibroblasts. Ultimately the cells, owing to the continued breaking-up of their bodies into fibrils, lose the greater part of their protoplasm and finally return to the stage in which they represent small, narrow cells with dark, spindle-shaped nuclei surrounded on all sides by fibrils.

Embryonal connective-tissue cells possess the faculty of active independent locomotion or ameboid movement.

Thus they are able, by means of globe-shaped or pointed pseudopods, to move about in the meshes of fibrinous networks, in minute cavities of porous foreign bodies, or, for example, in the meshes of corneal tissue that has been destroyed by a caustic. The forms produced in this way are often very bizarre and must not be confounded with leukocytes, which also possess the faculty of independent active movement; they are distinguished from the latter by their greater size and the vesicular nature of the nucleus, instead of the dark, lobulated, or fragmented nucleus of leukocytes (Plate 34, Fig. 1).

Certain other kinds of cells, however, which in their development closely resemble the fixed cells of adult connective tissue, may play an important part in the formation of new connective tissue. The proliferation of fibroblasts is not accomplished exclusively by derivatives of former connective-tissue cells; often endóthelial cells also take part in the process. The axiom quoted above, "*Omnis cellula e cellula ejusdem generis,*" is, therefore, subject to the limitation that derivatives of the mesenchyma which have undergone great differentiation and become endothelial cells of blood-vessels return to their original indifferent stage and may take part in the formation of an undifferentiated (connective-tissue) germinal tissue. In large collection of fibroblasts originating in vascular connective tissue the endothelial sprouts are, in fact, so intimately mingled with the newly formed cells descended from connective-tissue cells that it is practically impossible to distinguish the two kinds of elements (Plate 25, 3 and 6). Both contain an abundance of mitotic figures, and so long as the invading endothelial sprouts have not formed cavities filled with red blood-cells, they are absolutely undistinguishable from the spindle-shaped fibroblasts, which are also arranged in long, orderly rows. A similar part to that of the endothelial cells of blood-vessels is taken by the endothelial cells of lymph-vessels and lymph-clefts in the connective tissue.

It is a much-disputed question whether leukocytes derived from the blood are capable of taking an active part in the formation of tissue, whether they can produce fibroblasts, and later be converted into connective-tissue cells. The question was formerly answered in the affirmative by a number of investigators (Cohnheim, Metchnikoff), and it was assumed that the colorless blood-cells possess the faculty of changing to fixed connective-tissue cells and, therefore, of taking part in the building up of permanent tissue. But more recent investigations with improved methods have failed to give any support to the theory that such a conversion can take place (Marchand). The cellular elements from the blood are never capable of forming tissue in the body; they are incapable of forming intercellular substance or furnishing material for the building up of tissue. Even the eosinophil cells, which were by some supposed to possess a special faculty of producing connective tissue (Arnold, Marwedel), do not in reality possess that power (Enderlen). It follows, therefore, that connective tissue can be formed only from connective-tissue cells and from the genetically related endothelial cells of the vascular and lymphatic systems. That the latter take part in the production of connective tissue is beyond all doubt. Thus we have already seen in the organization of thrombi, for example, what an important part the endothelium may play in these processes.

The cells which take part in the proliferation of connective tissue possess, in addition to their faculty of independent movement, that of taking up corpuscular elements of every description. As they were credited with a destructive and digestive power over all organic particles, they were called "*phagocytes*" (Metchnikoff), and as they differed from the equally phagocytic leukocytes by their greater size, Metchnikoff, the discoverer of phagocytosis, called these elements, whose descent from connective tissue he, however, denied, "*macrophages*," in contradistinction to the leukocytes, which he designated "*microphages.*" Von Recklinghausen selected the more noncommittal term "*contractile cells*" to designate cells possessing the faculty of taking up foreign bodies into their protoplasm; for it must be assumed that both independent movement and the ability to take up foreign bodies depend on the contractile faculty of the protoplasm. By virtue of this faculty these cells play an important part in all processes that accompany molecular tissue disintegration, and in which the resulting particles cannot be assimilated directly by the cell-bodies. Foreign bodies of every description, both such as enter the organism from without and such as are formed by dead cells or parts of cells, may be taken up by the phagocytes. If, for example, a mixture containing foreign bodies in suspension (starch-granules or lycopodium spores) is injected into the peritoneal cavity of a guinea-pig, the connective-tissue cells of the peritoneum, especially of the omentum, very soon begin to exhibit an extraordinarily active cell-proliferation, the adventitial elements of the small blood-vessels particularly undergoing active multiplication and forming large cells very rich in protoplasm which attach themselves closely to the surface of the foreign bodies. Thus, for example, the lycopodium spores (Plate 34, Fig. 1) are covered with numerous crescentic and sickle-shaped cells, which at last completely surround the foreign body. Quite frequently the spores are found surrounded by protoplasmic masses containing several nuclei, and thus demonstrating themselves as giant-cells.

The formation of giant-cells or *polykaryocytes* may attend any new formation of tissue, but is found more particularly in the presence of foreign bodies that have entered the organism from without. There are two ways in which it may be conceived that giant-cells form, and, as a matter of fact, their mode of origin does appear to be dual; for giant-cells may be formed by repeated division of nuclei within the same cell, in which case the term "proliferation giant-cell" is used, or the giant-cells may be formed by the confluence and union of several preëxisting cells—so-called "conglutination giant-cells." It is needless to say that the fully formed giant-cell does not always show its mode of formation; when, however, the cell-body contains the remains of cell-walls, it is a sign that the giant-cell has been formed by the union of several cells. [Indications of distinct walls might also be interpreted as evidence of subdivision of the giant-cell into mononuclear or small cells.—Ed.] The bodies of these structures may in this way attain a very great size; they are either quite homogeneous in appearance or present numerous minute vacuoles. The nuclei may be large, vesicular, provided with a delicate framework of chromatin, and often present a distinct polar or bipolar arrangement; they are usually massed in greater abundance on the side opposite the incorporated foreign bodies (Plate 30, Fig. 5). It is rather remarkable that mitoses are observed in the nuclei only in exceptional cases, and it must be assumed, therefore, that direct division of the nuclei may take place in these structures also.

In addition to all these more or less polyhedral cells and giant-cells with oval, vesicular nuclei, every granulation tissue, every formation of new connective tissue, contains a mass of variously sized, circular cells. The protoplasm of these cells is usually distinctly granular, and is sometimes loaded with eosinophile granules or with granules that take a dark stain with the alkaline anilin dyes (methylene-blue). The nuclei are dark, circular, and often multiple; the chromatin-net and the framework contain large, shapeless granules of chromatin. These cellular elements are usually called *plasma-cells* (Waldeyer) (Plate 30, Fig. 2), and are held to include also the small mononuclear elements with a narrow, scarcely perceptible border of protoplasm, which are usually regarded as lymphocytes. Ranvier was the first to describe in the connective tissue of amphibious animals and mammals cells which, on account of their faculty of dividing both nucleus and cell-body by constriction, he called "*klasmatocytes.*" These structures are probably identical with the mast-cells first found by Ehrlich in connective tissue, and distinguished by the numerous granules imbedded in their protoplasm (E. Neumann). The plasma cells and lymphocytes are usually arranged in groups, often distinctly perivascular, and, taken altogether, they represent what is known as "*small-cell infiltration.*" The origin of this cellular material is not definitely known, and great differences of opinion exist as to whether it is derived in the last instance from the blood-current, escaping from the vessels by emigration, or whether it is descended from the fibroblasts—that is to say, originally from the connective-tissue cells. It would appear that a part, at least, of the small round-cells are derived from the blood and escape from the vessels by active emigration; for their perivascular arrangement is often very remarkable, and they are often found in the walls of the smaller blood-vessels. It is quite possible that a secondary division and multiplication by mitosis may take place; the division of the nuclei in the polynuclear forms is usually direct. There is no doubt that the small lymphocytes may, by swelling of their protoplasmic bodies, be converted into the larger forms—the plasma-cells. For a long time it was believed that at least a part of these cells are directly derived from the connective tissue (Unna). Ribbert believes that this small-cell infiltration is to be attributed chiefly to the foci of lymphocytes which are normally present in the corresponding situations, and to a swelling of their elements. In the light of the more recent investigations by Marchand an explanation of the small-cell infiltration, which is so important for the understanding of the proliferative processes in connective tissue, may be afforded by the assumption that "the blood-vessels are regularly accompanied by a number of cells which possess the faculty of producing elements of the nature of lymphocytes and the large mononuclear leukocytes, and that it is possible that these cells enter the blood-current and in that way really form leukocytes. The conversion into ordinary multinuclear cells, the formation of granules in the cells, the changes in the shape of the nucleus, are secondary processes which take place partly within the blood-current and partly, it may be, in certain organs—for instance, the bone marrow." Marchand applies the term "*leukocytoid cells*" to all the elements formed in this way outside of the vessels, and accordingly includes among them "both the small lymphoid cells of small-cell infiltration and the various modifications of plasma-cells, the mast-cells, and the large phagocytes of the serous cavities."

"*Mast-cells*" is the term applied to the elements so frequently observed in embryonal connective tissue, whose body protoplasm is densely covered with spheric granules which stain deeply with alkaline anilin dyes; these granules are usually of the same size in the same cell, but their size varies greatly in different cells. The best stain to bring them out is gentian-violet.

Lately, Maximow proposed the term "*polyblasts*" to include all those cells which appear in new formation of connective tissue and which are neither leukocytes nor fibroblasts. According to this author's simplification of the nomenclature this term includes cells which have been described by different observers under a variety of different names, as: mononuclear leukocytes, lymphocytes, wandering cells of connective tissue, histogenic wandering cells (including eosinophile cells), plasma-cells (Waldeyer, Unna), klasmatocytes (Ranvier), granulated cells or mast-cells (Ehrlich), and leukocytoid cells (Marchand).

In the last instance, then, all these "polyblasts" are colorless blood-cells derived from the blood-current, and they are responsible for the so-called "small-cell infiltration." Unlike the multinuclear leukocytes, however, they do not disappear from the inflammatory foci when they have once made their appearance; but after a fibrillar connective tissue has been produced by the fibroblasts, they remain among the bundles of collagenous intercellular substance and form so intimate a part of the scar-tissue that at last they cannot be distinguished from the true connective-tissue cells. They themselves never produce true connective tissue. Some of them take up a position on the outside of the endothelial tubes, representing the young blood-vessels, and are converted into granular adventitial cells (klasmatocytes). These polyblasts also furnish a large portion of the giant-cells that make their appearance chiefly after the introduction of foreign bodies.

The *regeneration of fatty tissue*—that is, connective

PLATE 26 a.

Laparotomy Wound, Two Weeks Old (× 40.): 1, Epidermis of the wound-edges; 2, connective tissue of the cutis at the edges; 3, embryonal, newly formed connective tissue between the edges; 4, newly formed blood-vessels; 5, regenerating sweat-glands; 6, adipose tissue; 7, fibrin among the deeper layers of the subcutaneous adipose tissue.

PLATE 26 b.

Laparotomy Wound, Two Weeks Old, Showing the Details of Plate 26 a (× 125.): 1, Old connective tissue of the wound-edges; 2, embryonal, newly formed connective tissue with fibroblasts; 3, newly formed blood-vessels; 4, newly formed low epidermis.

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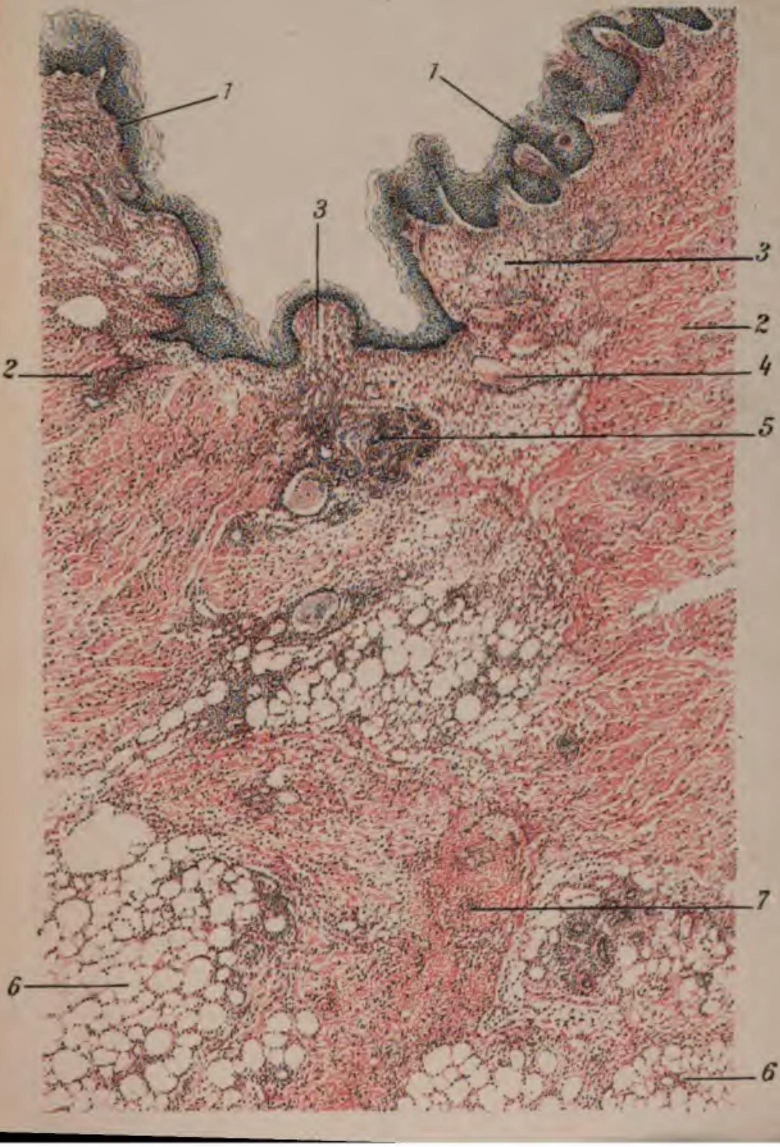
tissue modified by the infiltration of its cells with fat—is attended by the appearance of large, round or polyhedral mononuclear and multinuclear cells (fibroblasts) within the membranes which surround the original fat-cells; these cells are formed by continuous division from the former fat-cells or their nucleated protoplasmic remains, and often present an epithelial arrangement in places where the fat has disappeared.

The new formation of elastic fibers is a comparatively slow process. In wounds of the skin involving the corium or subcutaneous tissue regeneration of the elastic elements does not begin until four or five weeks later, and the new elements are always formed from old elastic fibers, never by the conversion of connective-tissue fibers. They grow at the border-line of the surviving bundles of fibers in the form of delicate, interlacing twigs, not, as a rule, from the ends of the old fragments, but from their sides, with which they form acute angles (Enderlen). Gradually they grow toward one another from both sides and unite to form a delicate network. But after months or years a very perceptible difference in the thickness of elastic fibers may be observed in old cicatrices of the skin.

Hand-in-hand with the formation of new connective tissue there is a production of blood-vessels which grow into the newly formed cellular material and form a considerable portion of the granulation tissue.

At first they appear at the side of the old surviving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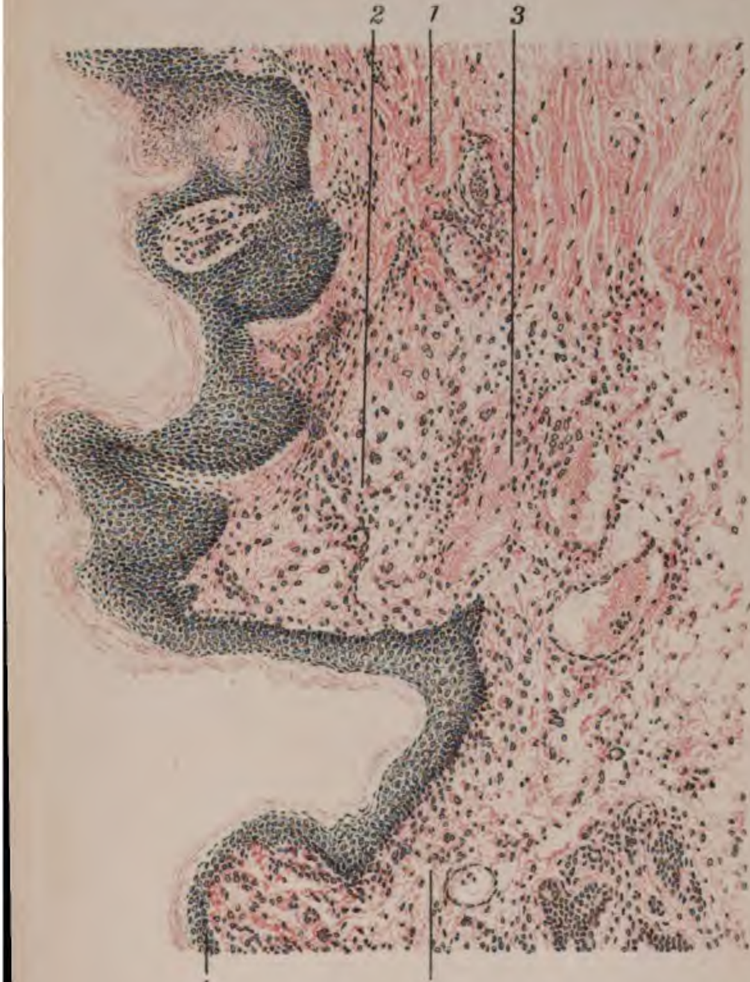
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capillaries in the form of minute, pointed buds consisting of spindle-cells with a fairly large amount of protoplasm and presenting the greatest resemblance to fibroblasts. The more recent investigations, however, force us to believe that these buds are to be regarded as true endothelial cells which have grown solely from preëxisting endothelium and continue to grow by mitotic division of their elements (Plate 25, 6). It has never been demonstrated that fibroblasts, the derivatives of fixed connective-tissue cells, are ever converted into endothelium; although, conversely, endothelial cells, as mentioned, unquestionably are converted in some cases into connective-tissue cells.

The endothelial buds at first represent solid cords of cells projecting into the newly formed tissue; canalization and further change are secondary processes that are effected later by the pressure of the blood from the old vessels pressing the cells apart and converting the compact mass into tubular cylinders. The individual buds grow toward one another and form connections with one another, and thus a ramifying vascular network is ultimately produced in the embryonal connective tissue. The vascular buds are usually accompanied in their growth by fibroblasts (and plasma-cells) arranged in regular rows along their outer side; the plasma cells adapt themselves closely to the endothelial cells and are later converted into the adventitial elements. The development of blood-vessels takes place simultaneously at many points, and at an early stage the newly formed tissue becomes extremely vascular; but it represents only a temporary condition. With the development of collagenous substance—*i.e.*, fibers—from the fibroblasts, the thin-walled, vascular endothelial tubes gradually disappear. They are compressed, their sides adhere and obliterate the lumen, until finally the endothelial cells are converted into fibrous connective tissue, while only the larger vascular trunks with thicker and already differentiated walls persist in the fully formed scar tissue.

To sum up once more, after this explanation, in the new formation of connective tissue, as it appears, for example, in a fresh wound of the skin or of the mucous membrane (tongue), we observe in succession the following processes (Plate 25): At first a circumscribed necrosis of the old tissue, due to the trauma, appears on the wound-edges; by the extravasation of blood and plasma the defect or gaping of the wound-edges is filled up and bridged over by fibrin, which at first is delicate and later becomes coarser in structure. At the same time there appear usually within the meshes of this fibrin numerous polynuclear leukocytes which have escaped by emigration from the greatly distended blood-vessels around the margin of the wound, where globular stasis or stagnation of the red blood-cells and peripheral disposition of the leukocytes may usually be demonstrated. Gradually new cellular elements make their appearance and grow into the fibrin, which they fill completely and for the most part consume as they continue to grow. These cells are spindle-shaped, stellate, or polyhedral, endowed with independent movement, have a fair amount of protoplasm, and are derived by mitosis from the old connective-tissue cells (fibroblasts). Some of this cellular material must also be regarded as formed from the endothelial cells of the old tissue. In addition there are found in variable numbers so-called plasma-cells—that is, large and small circular elements which probably grow chiefly from the adventitial cells at the edge of the wound, and which, either as small, mononuclear leukocytes or larger plasma-cells with granulated protoplasm and sometimes with several nuclei (leukocytoid cells, polyblasts), produce the so-called small-cell infiltration of the granulation tissue. The evolution of this cellular material is accompanied by the sprouting of endothelial cords which can be formed only from cells of their own kind and are later hollowed out by the inflow of blood.

The **regeneration of epithelial tissue** is usually quite complete in the case of injuries and destructions. Squamous epithelium gradually pushes its way over the gap in the tissue, which is first filled with fibrin and later with granulation-tissue. The first reactive phenomenon observed after an incised wound with smooth edges, for example, is the death of the epithelial cells within a certain distance of the wound-edges. The cells lose their nuclei, contract, and undergo desquamation. Immediately afterward, however, the nuclei in the contiguous cells enlarge and the chromatin framework and nucleus become more prominent. This is followed by active division of the nuclei, both by indirect mitotic and by direct division. Mitosis takes place chiefly in the cylindric basement layer and in the deeper rows of the Malpighian layer, not only in the peripheral zone of the wound, but also at some distance from the wound-edges. In addition some nuclear proliferation by direct division probably also takes place; thus, in the peripheral portions of a wound of the tongue (Plate 25, 1″), it is possible to see very clearly after four days, in the enlarged nuclei of the epithelial cells, reduplication of the nuclear invagination of the nuclear wall, constriction of portions of the nucleus, and finally complete division of the nuclei into two parts. Cells containing these directly divided nuclei are often found in close proximity to cells presenting mitotic figures, and, therefore, are not especially localized and have no special relation to the individual layers of epithelium. The intercellular cement-substance of the newly formed epithelium is not infrequently increased in breadth, and the ledges of protoplasm in these places are then unusually long and far apart. Sometimes leukocytes are seen to enter the newly formed epithelium, being distinguished by their dark nuclei, which contrast strongly with the lighter color of the intercellular cement substance.

A favorite object for the study of regeneration of epithelium is the cornea. In a warm-blooded animal superficial wounds of the membrance, involving only the epithelium, are usually completely covered with epithelium after twenty-four hours. If the traumatism is deeper, and in the case of penetrating wounds of the cornea involving the anterior elastic lamina (Bowman's membrane), the lamellæ of the corneal connective tissue and the posterior elastic membrane (Descemet's membrane), the defect is at first filled with a deposit of fibrin deri

PLATE 27.

FIG. 1.—**Punctured Wound of the Cornea in Man, After Two Weeks** (Alum-cochineal; van Gieson. × 40.): 1, Corneal epithelium at wound-edges; 2, lamina elastica anterior (Bowman's membrane); 3, corneal connective tissue; 4, cicatricial tissue, fairly thick, especially in the anterior portions, and merging gradually with the lamellæ of the cornea; in the posterior portion looser, more cellular, and arranged in more regular order; 5, numerous newly formed blood-vessels in the scar, growing out from the scleral vessels at the corneal border; 6, epithelial plug dipping in at the edge of the scar. To the right and above, remains of the folded Descemet's membrane.

FIG. 2.—**The Foregoing in Detail** (× 280.): Epithelium of intact corneal tissue contiguous to the wound; 2, membrana elastica anterior (Bowman's membrane); the cross indicates the point where the epithelial plug dips in toward the scar; 3, corneal connective tissue; 4, newly formed scar tissue; 5, vessels that have grown through the cornea from the scleral border; 6, regenerated epithelium over the scar, with distinct prickle-cells; 7, leukocytes among the epithelial cells; 8, nuclei of fibroblasts; 9, newly formed vessels in the granulation-tissue.

from the aqueous humor. This is then bridged over by the rapidly proliferating epithelium, which dips in at the margin of the anterior elastic membrane, somewhat in the shape of a plug. This downward growth persists after the fibrin has been replaced by granulation-tissue and even by embryonal fibrous tissue and the continuity of the membrane has been restored (Plate 27, Figs. 1 and 2). Here also it is common to find multinuclear epithelial cells, especially in the cylindric basement layer, which are probably produced chiefly by direct division; for the frequency of mitotic figures is by no means proportionate to the rapidity with which the defect is covered with newly formed epithelium. Here also isolated wandering leukocytes are found in the broad bands of cement substance between the epithelial cells.

Not infrequently the gradual epidermization of a large wound, especially when the underlying granulation-tissue is irregular in its growth and tends to form unusually tall elevations and correspondingly deep depressions is accom-

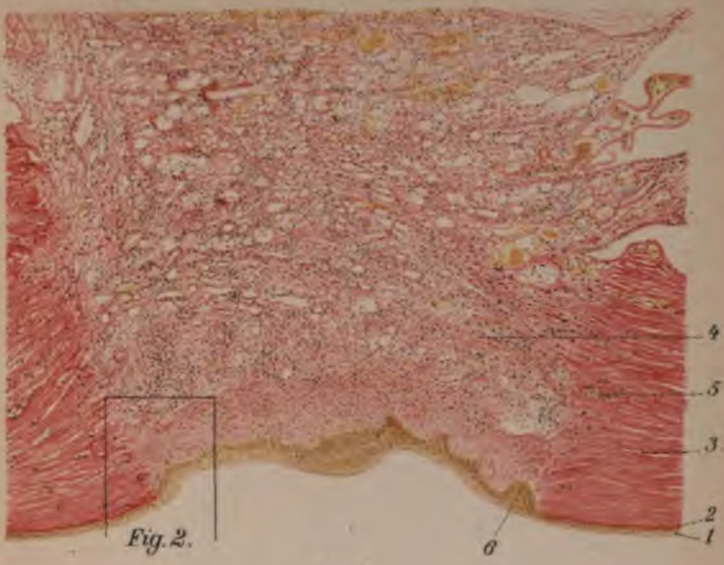
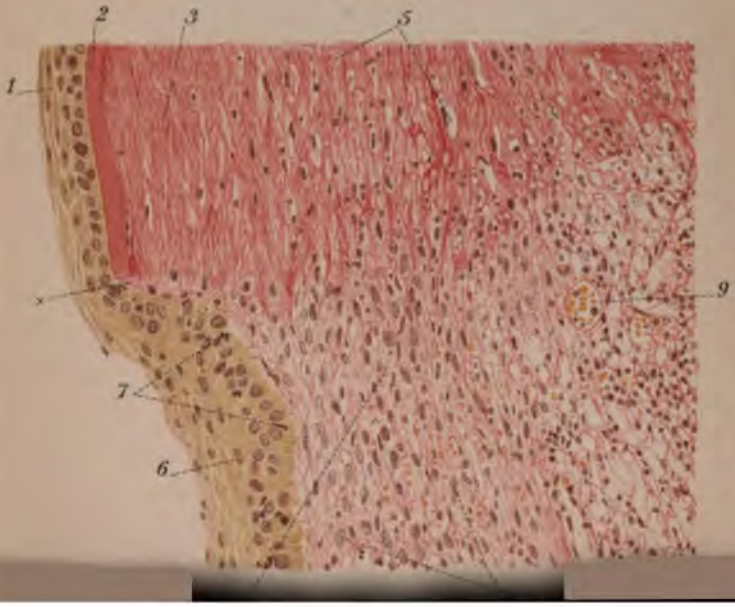


Fig. 1.



panied by the formation of epithelial plugs which are sometimes branched and extend deeply into the tissue, sometimes below the level of the surrounding epidermis. Owing to their numerous ramifications they appear in sections to consist of single epithelial islands completely cut off from their surroundings. But this isolation from the surrounding tissue is only apparent, as a series of sections will at once show; in every instance connections with the superficial epithelium can be demonstrated, although they may be exceedingly delicate. These formations are called *atypical epithelial proliferations* (Friedländer). They are found with a special frequency at the edges of ulcerations (crural ulcers) or of wounds produced by cauterization or burns. Sometimes well-developed, concentrically arranged horny pearls are found in these atypical epithelial proliferations; these were formerly called cancroid pearls, because their formation was regarded as characteristic of carcinoma of the skin; but they occur also in perfectly benign epithelial proliferations, whenever a thick layer of squamous epithelium, possessing the faculty to form keratohyaline granules and later to undergo complete cornification, is imprisoned within the depths of the tissue (Plate 66, Fig. I).

In addition to this new formation of epithelium at the edge of the wound—*i. e.*, by the proliferation of the marginal epithelial cells, a so-called "*insular*" *epidermization* sometimes takes place by the growth in the midst of the granulation-tissue of insular areas of epithelium completely cut off from the marginal epithelium. Sometimes it is merely due to a secondary accidental interruption of the original connection with the marginal epithelium; but in many cases there has never been any connection, and in these cases the only explanation for the process is that the epithelial islands grow from the remains of the excretory ducts of sweat-glands and from hair-follicles; for these glands are situated deep within the cutis and may, therefore, escape a superficial injury. As the epithelium of their excretory ducts is in every respect identical with the superficial epithelium, it may proliferate and thus

PLATE 28.

FIG. 1.—**Muscle Wound in the Rabbit After Four Days** (Iron-hemat.; Heidenhain eosin. × 300.): 1, Spindle-shaped muscle-cells; 2, budding figures in the nuclei of muscle-cells; 3, transverse sprouts from nuclei; 4, multinuclear muscle-cell tubes; 5. formation of longitudinal and transverse striation.

FIG. 2.—**Incised Wound in Rabbit-liver After Seven Days** (Hemat.; van Gieson. × 80.): 1, Liver tissue at the edge of the wound; 1′, central vein; 2, necrotic liver tissue; 3, newly formed embryonal connective tissue; 4, newly formed gland-like tubes of bile-ducts; 5, cystic dilatations of the foregoing; 6, newly formed connective tissue.

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form a covering with stratified cylindric epithelium. In artificially produced wounds of the skin or mucous membranes, if the glands are carefully and thoroughly destroyed, this insular epidermization is never observed.

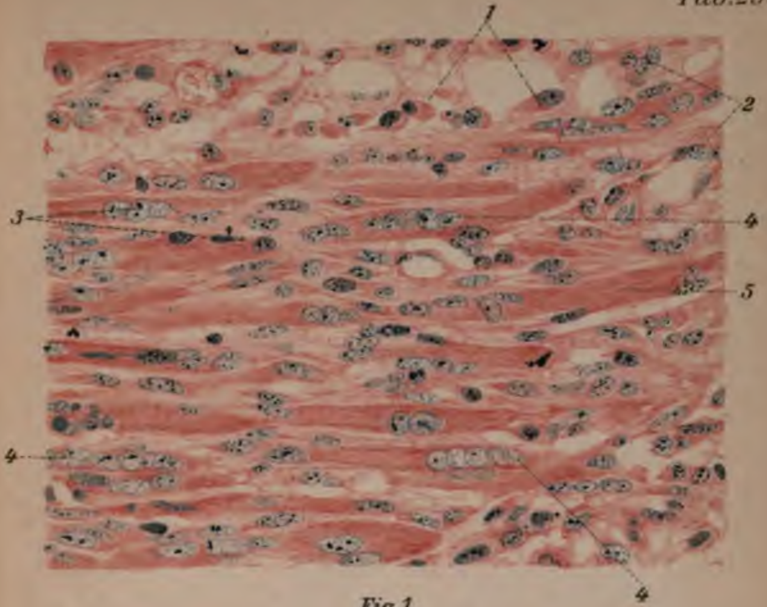
The regeneration of cylindric epithelium is almost always accompanied by changes in the shape of the individual epithelial cells; at first the elements are low, squamous or polyhedral, and later again become cylindric cells. This integumentary tissue possesses considerable power of regeneration, as, for example, after loss of the tissue in the trachea and bronchi in diphtheria, in the stomach in the healing of a round ulcer, and in the intestine in the healing of typhoidal ulcers, and occasionally in the partial healing of tuberculous ulcers.

Glandular epithelium also is possessed of considerable power of regeneration so long as remains of the old glands survive; the cells then continue to proliferate from these remains, and the resulting substitutes may attain complete functional power.

The new formation of several important kinds of tissue will now be described briefly.

Striated Muscle.—After traumatic or chemic destruction of striated muscle-tissue the first change is a circumscribed necrosis at the point of injury, the contractile substance being converted into homogeneous, irregular clumps. In the contiguous portions the muscle nuclei undergo rapid multiplication, evidently by direct

Tab.28.



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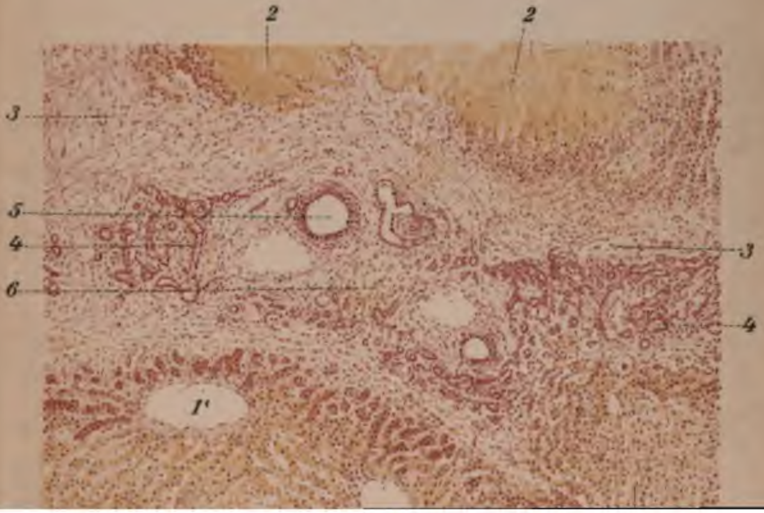

division—that is, by constriction. In this way long chains of nuclei are formed. The nuclei accumulate at the ends of the stumps of the fibers, which are often club-shaped and are then designated "*muscle-buds*" (Neumann). Sometimes a longitudinal splitting is later observed in these buds. The newly formed nuclei now surround themselves with protoplasm, and circular or spindle-shaped cellular structures with intensely granular bodies are formed, and as these grow and arrange themselves in ribbon-shaped structures, the so-called "*muscle-cell tubes*," result (Waldeyer) (Plate 28, Fig. 1). The nuclei show distinct budding; the buds grow not only longitudinally, but also transverely, so that we have rows of nuclei lying side by side. Later, the protoplasm becomes fibrillar, the longitudinal striation appearing before the transverse; the latter appears first in the form of minute granules arranged side by side in orderly rows. Later the nuclei, which at first occupy the middle of the fiber, take up a position nearer the surface, and the intervals between them increase. Not until this stage is reached do the fibers surround themselves with a new envelop of sarcolemma which is probably formed from the surrounding connective tissue. The process is, of course, accompanied *pari passu* by simultaneous new formation in the intermuscular connective tissue which does not differ in any essential point from regenerative processes of simple connective tissue.

Wounds of the *heart-muscle* practically always heal exclusively by means of connective-tissue scars and never by the new formation of muscle tissue. As in the case of infarcts of the myocardium, a non-perforating solution of continuity occurring secondarily to traumatic degeneration of the muscular elements gives rise to the formation of a granulation-tissue derived from the intermuscular vascular connective tissue, which is ultimately followed by sclerotic induration containing very few nuclei.

In the contiguous parts of the muscle the nuclei may temporarily show a multiplication, and muscle-cell tubes may even be formed; but the regeneration of contractile substance is never extensive, and its continuity is never restored.

In the case of **bone tissue** a solution of continuity or the amputation of a long bone is followed first by more or less extensive hemorrhage into the medullary cavity and surrounding periosteum; later the coagulation of fibrin takes place. In the case of fractures the union of fragments is not effected by the immediate formation of new bone, but by a complicated proliferative process, beginning both in the periosteum and in the medullary cavity. These parts produce a mass which greatly exceeds in size the diameter of the bone and is known as the *callus*. This callus formation is at first purely of the nature of connective tissue, but changes later, first into cartilage and then into bone. The healing of bone, therefore, represents a process similar to the original formation of bone, and the closure of an amputation wound is also preceded by the development of a robust, apparently excessive, new formation of tissue from the periosteum and medullary cavity. The connective-tissue cells of the periosteum, especially those of the inner osteogenic layer, swell up and multiply, and numerous mitotic figures are observed. The blood-vessels take part in the process, and a granulation-tissue very rich in cells is formed at the ends of both fragments and grows through the intervening hematoma or the deposit of fibrin to which the extravasation of blood has given place; in this way a provisional union between the ends of the fragments by means of a soft, non-resisting tissue is brought about. At the same time an active proliferation of connective-tissue cells begins in the medullary cavity and leads to the formation of a tissue rich in spindle-cells which grow from both directions, and unless the displacement of the ends of the fragments is very great or there is some interposition of tissue, the two masses soon unite. This granulation-tissue then forms fibers and eventually produces a fibrous tissue poorly supplied with nuclei. This represents the fully formed connective-tissue callus, in which we distinguish the periosteal and the myelogenic callus. The callus, of course, obstructs the lumen of the medullary cavity and the adipose tissue in the cavity of the bone is replaced by ordinary fibrous connective tissue. If the surfaces of the fracture are not in contact and a certain distance remains to be bridged over by the callus, consisting of granulation- or connective tissue, the so-called *intermediary callus* is formed (Plate 29, Fig. 2). The fibrous substance is gradually converted into cartilaginous tissue by a fusion of the fibers into a homogeneous hyaline mass, representing the cartilaginous ground-substance; the cells are imprisoned in the circular cavities of this ground-substance and ultimately form cartilage-cells. At this stage the callus is cartilaginous and all its parts undergo this cartilaginous change.

The cartilage-cells now form a kind of hard secretion impregnated with calcium salts, which gradually surrounds them (Gegenbaur); at the same time part of the cell-body is included in the ground-substance of the bone, and the cartilage is thus converted into osseous tissue. The cells shrink, become spindle-shaped or stellate, and after a time send out wavy processes into the bone-substance; this completes their development into true bone-corpuscles. In the case of the periosteal callus the preliminary cartilaginous stage may be dispensed with and an osseous periosteal callus may be formed directly through the agency of osteoblasts, which, after arranging themselves in rows like epithelial cells, excrete a calcareous bone-substance which finally surrounds them and thus ultimately converts them into bone-corpuscles. At first the bony callus produces a marked thickening of the bone, from excessive deposition of tissue; but as the osseous substance in the cortical layers consolidates, the tissues in the remaining portions gradually atrophy and undergo absorption through the activity of *osteoclasts*, as happens when the medullary cavity is formed in the course of normal ossification. Multinuclear giant-cells take up a position along the bone-trabeculæ, and in some way that has never been explained cause a local absorption (Howship's lacunæ), thus gradually removing the portions

PLATE 29.

Figs. 1, 2.—**Death of Epidermis in Transplanted Skin After Reverdin-Thiersch** (Iron-hemat.; Heidenhain eosin. × 280.); Fig. 1.—1, Desquamated horny layer; 2, densely packed epithelial cells; 3, leukocytes; 4, large, vesicular spaces in the epithelium; 5, deep, elongated layers of the epithelium.

Fig. 2.—1, Desquamated horny layer; 2, densely packed epithelial cells; 3, vesicular and canal-like cavities in the intervals between the necrotic epithelial cells; 4, nuclei of epithelial cells with disappearing chromatin.

Fig. 3.—**Callus from the Femur of a Rabbit After Eight Days** (Carmin-bleu de Lyon. × 16.): 1, Cortical layer of the femur; 2, adipose tissue in the marrow; 3, connective-tissue and cartilage formation within the medullary cavity; 4, cartilaginous callus formed from the periosteum; 5, cartilaginous intermediary callus.

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which have become superfluous now that the cortical layer is formed, both in the periosteal and in the myelogenic callus. The swelling disappears, the periosteum again covers the bone, the medullary cavity becomes patulous and is surrounded only by trabeculæ of spongy substance, while the marrow itself also undergoes regeneration, during which it takes up fat from the connective-tissue cells and receives blood-vessels from the neighboring tissue. After a few months the site of the fracture often reveals itself only by a slight thickening of the periosteum.

Liver.—Wounds of the liver are followed by death of a contiguous portion of the organ, the extent depending on the kind and degree of the injury. As soon as the defect has been bridged over by the mass of fibrin formed by extravasated blood and plasma, it is gradually filled up by a granulation-tissue which grows from preëxisting connective tissue. Some epithelial elements, however, also enter into the formation of the new tissue, for the bile-ducts send out numerous buds into the tender young scar, which at first is poor in fibers, and there form a system of branching and interlacing canals. Sometimes large, cyst-like cavities are formed, surrounded on all

Tab.29.

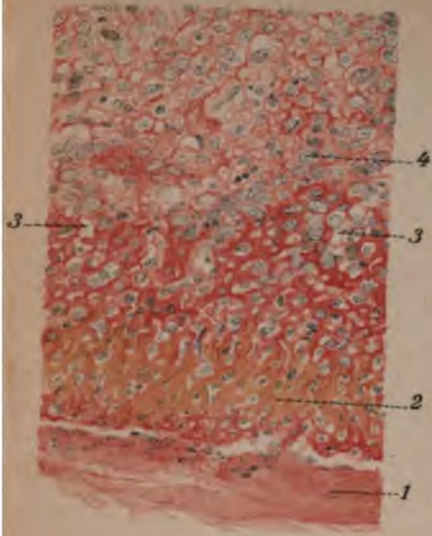


Fig.2.

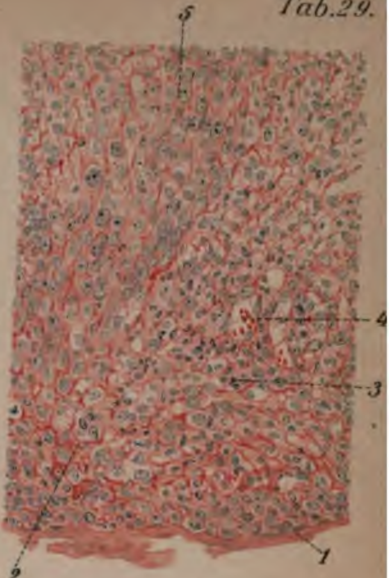
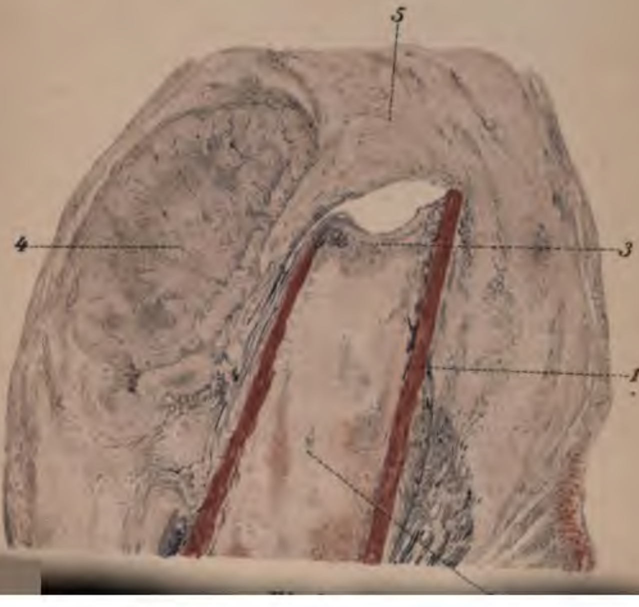


Fig.1.



sides by epithelium. The rows of epithelial cells may be so closely applied as to form a tissue which in its structure resembles liver tissue, but true regeneration of glandular substance capable of functionating probably never takes place. The scar from an incised wound of the liver in the rabbit after a week presents the following picture (Plate 28, Fig. 2): A large portion of the liver-tissue is necrotic, the cords of liver-cells are disintegrated and converted into a yellowish, homogeneous mass devoid of nuclei or filled only with the minute remains of nuclei. Growing from the edges of this area a loose-meshed connective tissue has already bridged the gap between the two edges of the wound. This young cicatricial tissue is traversed by numerous thin-walled, dilated vessels, and in many places incloses small groups of necrotic liver-cells which are distinguished chiefly by the presence of small particles of bile-pigment. This granulation-tissue contains in its interior a system of communicating epithelial tubes of varying caliber; some of the epithelial elements are low, almost squamous; others are cuboidal, but none of them presents a cylindric shape. In some places large, circular cystic cavities are seen in transverse section, recognized by the fact that their walls are lined with two or more layers of low epithelial cells. In places these tubes of cells come into direct contact with surviving portions of the liver-tissue. Mitotic figures are scanty, and do not occur at all in the liver-cells. Frequently small collections of necrotic liver-cells are seen in immediate contact with the epithelial canals, which appears to show that the latter do not take their origin from the cells of the hepatic parenchyma. Old scars in the liver consist almost exclusively of robust, fibrous, cicatricial tissue with few nuclei and containing a few scattered epithelial cysts. After the extirpation of considerable portions of the liver a similar cicatricial process takes place, in which, however, the capsular connective tissue takes the principal part. The surviving portions of the liver undergo marked compensatory hypertrophy, the acini enlarge, the liver-cells increase in number and present mitotic division of their nuclei, so that the loss of volume is completely made good in a comparatively short time (Ponfick).

A cicatrix following a wound of the **kidney** also presents in its connective tissue after eight to ten days newly formed narrow tubules which communicate with the straight and convoluted uriniferous tubules in the neighboring tissue (Barth). In the case of the kidney also there is no regeneration of functionating parenchyma.

In the **sexual glands,** the testicles and ovaries, also, the reparative process consists in simple scar-formation, and the destroyed parenchyma is never restored.

Nerves.—The reparative processes that take place in the nerves are of great practical importance. The peripheral nerves are capable of extensive regeneration. Not only after simple division of the nerve, but even after the excision of a considerable portion, nerve-conduction may be completely restored, showing that the nerve-substance evidently has been restored. Every solution of continuity in a nerve is invariably followed at once by degeneration of the entire peripheral and a variable portion of the central segment. When the peripheral portion is completely removed, as in the case of amputation of a limb, for example, the stump heals with the formation of connective tissue; even in this case, however, a proliferation of nerve-fibers regularly takes place and leads to the formation of a mass of interlacing medullated axis-cylinders, a phenomenon which was formerly erroneously included among the true tumors and designated an "*amputation neuroma*" or "*stump neuroma*" (see under Neuroma in the chapter on Tumors). In addition to the traumatic degeneration which follows division of the nerve-trunk and affects only the portions in the immediate neighborhood of the point of division, so-called secondary degeneration or paralytic degeneration sets in and progresses along the entire peripheral portion of the fibers, the medullary sheaths and axis-cylinders are gradually split up; in the central portion this process extends at least so far as the *next node* of Ranvier, and often for some distance farther.

Two days after the injury the medullary sheath breaks up into cylindric fragments which continue to split up into smaller and shorter fragments within the sheath of Schwann. The axis-cylinder also breaks down; first it swells up and presents small cystic and villous projections along its sides, and the fragments undergo varicose dilatation, while the myelin fragments present a frayed appearance. The degeneration of the axis-cylinder is accompanied by active proliferation of the nuclei in the sheath of Schwann. They enlarge, acquire more chromatin, and eventually are pushed to the center of the fiber among the fragments of myelin, very much as in the case of the nuclei of muscle-fibers. The protoplasm immediately surrounding the nucleus swells, so that the intervals between the myelin drops are occupied by cellular tubes possessing many nuclei, which continue to undergo mitotic division. It has never been satisfactorily demonstrated what part these cellular tubes, which later are converted into long-drawn-out, spindle-shaped elements by an increase in their protoplasm, play in the regeneration of nerves—whether they produce only the sheath of Schwann for the new nerve, or whether they have any connection with the new formation of the conducting fiber of the axis-cylinder and form a necessary substratum for it, as has been recently suggested by Marchand.

According to a more widely accepted view, the cord-like accumulation of cells which results from the sheath of Schwann forms, as it were, the path for the nerve-fibers. It is certain, at least, that the axis-cylinder grows only from the surviving portion of the central stump. Sometimes an old axis-cylinder throws out several delicate, spiral branches, one coiled within the other. The young fibers early receive a covering of delicate medullary sheaths [which by some are traced to the cells from the neurilemma.—Ed.] Conduction is restored through the newly formed axis-cylinder not only after smooth division of the nerve, but also after the excision of a considerable portion; this is shown by the fact that the peripheral part in every case and without reference to the size of the excised portion is doomed to destruction and must be restored by complete new formation.

In contrast to the great power of regeneration observed in peripheral nerves after their traumatic destruction, the faculty of the *central nervous system* to restore parts that have been destroyed is exceedingly slight. Both in the spinal cord and in the brain injury and destruction by other causes, such as hemorrhage, softening, or compression, is never followed by regeneration of the destroyed nerve-substance. In the case of a "healing," the resulting tissue, which may be formed quite rapidly, consists exclusively of connective tissue and neuroglia. Thus in dogs Schiefferdecker observed firm union of the ends of the spinal cord by connective tissue as early as two weeks after the division.

Skin.—Finally, a few words in regard to the histologic behavior of transplanted skin may not be amiss. It has been learned from investigations of the healing of transplanted portions of skin after the method of Réverdin and Thiersch, as well as of larger skin-flaps, that the greater part of the transplanted tissue is irrevocably doomed to destruction, which is contrary to the former view that actual direct union of the implanted piece takes place. In some cases the structure of the entire implanted flap presents evidences of such complete reconstruction as inevitably to lead to the conclusion that the flap acts only as a kind of natural plaster which stimulates and facilitates the formation of new elements from the surrounding tissue.

The epidermis in particular is almost always found to be destroyed completely in practically all its layers. The stratum corneum first separates and is cast off; this is followed by loosening and swelling of the superficial layers of the rete Malpighii. Irregular cystic cavities appear in the cells, and the cell-bodies appear to fuse into a coherent, almost homogeneous mass, which, however, stains with varying intensity in the different layers. The nuclei are forced out of the mass, so to speak, and are found collected in large and small, irregular and cystic, canal-like cavities (Plate 29, Figs. 1 and 2). The cells of the lower layers of the rete Malpighii often appear drawn out lengthwise, cylindric or spindle shaped, and narrow, "so that the deeper layers of the epidermis present a striation perpendicular to the surface" (Marchand). At first the nucleoli appear particularly dark and large (Plate 29, Fig. 1); later, however, a progressive loss of chromatin begins, and eventually the nuclei become pale, while the outer layers contain very small, almost unstained particles of nuclear matter. The leukocytes traverse this dying epidermis and are found collected in places in large cystic cavities. Red blood-cells also may be washed into the communicating, canal-like cavities. The tissue of the transplanted cutis undergoes progressive degeneration, which begins the first day after the operation, and at the same time leukocytes and plasma-cells make their way into the tissue. The spindle-cells of the connective tissue shrink and ultimately disappear, as do also the nuclei in the walls of the blood-vessels, especially the endothelial cells. From the underlying tissue embryonal connective-tissue cells and blood-vessels now push their way outward, and in their progress they consume the layer of fibrin between the implanted flap and the base; the blood-vessels of the flap again fill with blood, the young blood-vessels utilizing many of the older channels and growing directly into the dead endothelial tubes. Even the elastic elements of the implanted skin-flap, which naturally possess considerable powers of resistance, are also gradually destroyed after having been pushed aside and broken up into fragments. New elastic fibers grow in from the side in the same way as in the case of new formation of elastic tissue, which has been described elsewhere.

The destruction of the transplanted portion and its replacement by new tissue is not a sudden process, nor is it uniform in every portion of the denuded surface. The part which forms most rapidly is the epithelium, which grows in from the sides under the protection of the dying epidermis. Sometimes, however, if vascularization takes place early enough, a few isolated groups of cells survive in the deeper portions of the transplanted epidermis, and in such cases these surviving cells, of course, may start a regenerative process; and when a large, thick flap of skin is transplanted, a new formation of cells may begin in the ducts of the sweat-glands.

According to Karg, the pigmentation of transplanted skin in dark-skinned individuals is effected by chromatophores—*i. e.*, stellate, pigment-containing, wandering cells; the latter traverse the cutis, and with the aid of their processes, which grow in between the cells of the epidermis, deposit their pigment in the latter.

INFLAMMATION.

Inflammation is a faculty, phylogenetically acquired by adaptation, by virtue of which the body reacts to injuries of tissues in such a way that the sum-total of the reactive phenomena neutralizes as much as possible the effects of the injury.[1]

It follows, therefore, that: 1. Inflammation in itself is not a morbid condition, but merely represents the symptom of a morbid condition; just as fever, for example, is not a disease, but the expression of the reaction on the part of the body to an irritant.

2. Anything that is capable of injuring tissues may produce inflammation.

It has been seen that certain injuries, when they affect the tissues, may lead to the occurrence of retrogressive metamorphoses, manifesting themselves either as degenerations, as necrosis, or necrobiosis of cell territories, and that these changes are regularly followed by certain reactive phenomena in the surrounding tissue, unless restitutio ad integrum rapidly ensues or the retrogressive metamorposis is so intense and so extensive, or occurs in organs of such importance, as to cause the death of the entire organism within a short time. In such cases the

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[1] As a matter of fact, even the lowest unicellular organisms, such as amebæ, manifestly react to injurious influences (chemotaxis, phagocytosis, intracellular digestion), while in the higher forms of life these *reactions* are performed by certain definite cell-groups.

"inflammatory" processes are produced not so much by the injury itself, as indirectly by the injured or dead tissue, which in itself acts as an irritant to the neighboring cells and tissues. Thus, for an example, it has been seen that infarction is followed by "*reactive inflammation*," culminating in the replacement of the essential tissue of the organ by connective tissue. At the very beginning of this process the necrotic portion of tissue is surrounded by a wall of leukocytes, which also extends some distance into its interior; later, as the dead tissue breaks down, newly formed granulation-tissue pushes its way into the mass. Some parts of the tissue suffer fatty degeneration and eventually undergo complete solution and absorption; but even these are replaced by the formation of new tissue, which ultimately fills up the gap. The same thing happens in the case of any defect produced by injury or any other cause. The thrombus formed in a blood-vessel ultimately becomes a dead foreign body and stimulates the contiguous vessel-walls to proliferation, the tissue thus produced eventually replacing the thrombus. In this sense any mechanical, chemic, or thermic influence may be said to cause inflammation in the tissue, but a retrogressive process is not always necessarily present in the tissue at first. In the greater number of cases it is not observed at all, or occurs only later on, and the inflammatory phenomena develop immediately after some external injury to the organism. Although the irritant is itself the direct cause of the inflammation, the essential thing about it always is that it injures the tissue. Inflammation occurs because tissue has been injured; the body stands on the defensive against injury, and this defensive processs manifests itself to the observer in the variegated picture of inflammation. If the noxious substance or influence is completely removed from the body, the inflammatory process may be said to have a certain "physiologic" course. The "healing process," which is ushered in by the inflammation, becomes complete; but if the noxious agent cannot be removed by the reaction of the body, the latter is gradually destroyed, and the phenomena of inflammation continue to the end. This is more particularly the case in the presence of these noxious bodies that constantly reproduce themselves spontaneously within the organism, and possess the faculty of spontaneous multiplication—in other words, that are alive—the parasitic and especially the bacterial causes of inflammation. There is no justification in saying, therefore, that an individual dies as the result of suppuration in various organs (septicopyemia); it would be more correct to say that the individual dies of a staphylococcus or streptococcus infection *in spite of* the development of multiple and extensive suppurative processes.

What means has the organism at its disposal to react to injuries and defend itself against them? The doctrine of inflammation, which in many ways is an index of the entire history of medicine, was dominated, until well into the past century, by the views of Celsus and Galenus that the inflammatory process consists in an engorgement of the tissues, and from this conception the cardinal symptoms, *calor*, *tumor*, *rubor*, and *dolor* (heat, swelling, redness, and pain) were derived, to which later was added *functio læsa* (impaired function).

By a most laborious process, which I shall not attempt to trace here and which is marked chiefly by the epoch-making investigations and discoveries of Virchow, von Recklinghausen, Cohnheim, Ziegler, Marchand, and others, our views have at last been clarified, and it is now generally conceded that inflammation is anatomically characterized by three main processes, traceable both macroscopically and microscopically, namely: (1) Exudation; (2) emigration; (3) cell-proliferation. The two former have their origin in the vascular system, or, to be more exact, in the contents of the blood-vessels. In every case of inflammation the three processes are at least indicated, if not actually present; very frequently one of the three predominates, and, partially at least, more or less obscures the other two, so that, according to the preponderance of one or the other of these symptoms, we distinguish in the *anatomic picture*: (1) *Exudative;* (2) *purulent;* (3) *pro-*

ductive inflammation. The third main division—primarily productive inflammation—must be carefully distinguished, however, from the forms of tissue-production which may occur secondarily to any other inflammation. In the case of exudation the tissue-production ultimately leads to organization of the exudate; but after purulent inflammation, when the pus and the dead tissue have been removed, the formation of tissue effects the restoration of the resulting defect. It would be useful to make a special division of the productive phenomena—*i. e.,* those processes which take place in fixed tissue-cells as distinct from those which have their origin in the vascular system, and to regard the latter alone as characteristic of inflammation. It has been seen, however, in the section on Pathologic Organization and Regeneration, that these processes, although quite different in their origin, are so closely connected that for the present such a division does not appear to be feasible.

Virchow, in his attempt to separate the conception of the inflammatory process from the vague notion that merely the vascular system and the blood were in some way concerned in it,—so-called "phlogosis" and "phlebitis,"—and to bring it into relation with the phenomena observed in cells, distinguished *parenchymatous inflammation* and *interstitial inflammation.* The former he traced to the clouding and increase of the protoplasm due to nutritive irritation (cloudy swelling); he believed that the tissue elements underwent a progressive change with a tendency to subsequent degeneration without the formation of an exudate between the cells. It is quite true that parenchymatous organs may present processes which, in addition to cloudy swelling, are characterized by a marked proliferative activity on the part of the parenchyma cells. The liver, for example, after certain forms of poisoning (Plate 33, Fig. 1), presents a marked cloudy swelling when examined in the recent state; but when a stained specimen is examined, the characteristic dissociaare enlarged and usually contain one or more nuclei—even two, three, or four nuclei are found in one cell. Mitotic figures are rarely seen; while, on the other hand, the shape and grouping of the nuclei indicate the occurrence of direct division. Figures exhibiting sprouts and division by constriction are abundant; the acini appear enlarged; the cells of a single acinus increase in number,—phenomena which, taken altogether, point to an increased production of parenchyma cells. But all these processes are merely temporary. Unless death occurs from some other organic lesion, they speedily give place to more profound destructive processes; necrosis with fatty degeneration sets in; or, if healing takes place, the lost tissue is replaced by granulation-tissue, and this is followed later by induration of the organ.

From the clinical viewpoint the conception of parenchymatous inflammation is even more deeply rooted. The clinician speaks of inflammation in many cases in which pathologically only degenerative processes can be demonstrated; thus, for example, the appearance of albumin or morphologic elements in the urine is regarded by the clinician as the symptom of renal inflammation, although these symptoms in a majority of cases are due to retrogressive metamorphoses and do not necessarily imply the slightest trace of inflammatory change. Nowadays pathologists can readily dispense with the conception of parenchymatous inflammation, and may include the processes formerly described under that name among the various forms of retrogressive metamorphosis, which have been minutely described in the preceding pages.

It is needless to say that even with our present view in regard to the nature of inflammation we cannot afford altogether to discard the notion that degenerative processes play a certain rôle, especially in the earlier stages; and it is probable that every case of inflammatory exudation and emigration implies the existence of primary degenerative processes in the vessels. The fluid inflammatory exudate contains a large percentage of albumin, almost *equal to that* of blood-serum. This phenomenon cannot be attributed altogether to an increase in the blood-pressure, for even in cases of excessive blood-pressure from intense passive congestion the transudate contains only a small quantity of albumin. The increase in the percentage of albumin must be chiefly due to some change in the filtering membrane—*i.e.*, the vessel-wall; and it is probable that these degenerative processes primarily attack the cement substance between the endothelial cells and later perhaps the cells themselves as well.

EMIGRATION AND PURULENT INFLAMMATION.

The first change observed in an inflamed area seen in a transparent living object, as in the mesentery of the frog, or, in the case of mammals, in the outstretched wing of the bat, is a slowing of the blood-stream. In the venous and capillary vessels the peripheral zone of plasma disappears and is replaced by white blood-cells. Cohnheim, the discoverer of emigration, attributed this emigration to an active process on the part of the leukocytes, but Hering and his followers showed that the phenomenon is of a purely physical nature; for it can be demonstrated that whenever corpuscular elements are suspended in a fluid which circulates in a closed system of tubes, retardation of the current causes the peripheral disposition first of the lighter elements, and, if the velocity is still further diminished, that of the heavier particles. The leukocytes, by virtue of their agglutinative faculty or the peculiar serrated nature of their surfaces, adhere to the inner wall of the endothelial tubes, sometimes roll along for a certain distance, and eventually stick fast, either singly or in little groups or clumps. Later the leukocytes are flattened against the inner surface of the vessel-wall. One side becomes flat and attaches itself closely to the vessel-wall, while the other side, that turned toward the lumen, may still preserve a convex outline. This phenomenon is attributed to the peculiar movement of their protoplasm with which leukocytes react to any movement of the surface, a tactile sensibility (Massart

PLATE 30.

FIG. 1.—**Leukocytes from a Recent Abscess in Muscle** (Hemat.-orange. × 625.): 1, Multinuclear leukocytes; 2, leukocytes with fragmented nuclei; 3, lymphocytes.

FIG. 2.—**Wandering Cells from the Connective Tissue of a Nasal Polyp** (Hemat.-eosin. × 625.): 1, Eosinophile, mononuclear, and multinuclear leukocytes; 2, large mononuclear leukocytes without granulation.

FIG. 3.—**Mast-cells from Lupous Granulation Tissue** (Carmin; gentian-violet. × 1500.).

FIG. 4.—**Fibroblasts from the Connective Tissue in the Ear of a Rabbit Three Days after Painting with Iodin** (Iron-hemat.; Heidenhain eosin. × 625.): 1, Spindle-shaped fibroblasts; 2, stellate fibroblasts; 3, multinuclear fibroblasts; 4, mitotic figures.

FIG. 5.—**Foreign-body Giant-cell Containing Scales of Horny Cells from a Case of Lupus Hypertrophicus** (Carmin-Gram. × 625.).

FIG. 6.—**Tuberculous Giant-cell with Pseudopods, from a Case of Tuberculous Peritonitis** (Hemat.-eosin. × 625.).

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and Bordet). The flattened side then sends out small protoplasmic processes or pseudopods, which penetrate the vessel-wall and gradually work their way through. When the extremity of the process has reached the outside of the wall, it swells out in the shape of a button, gradually enlarges more and more, and ultimately draws the entire cell through the wall; the little clump of protoplasm appears to develop a flowing movement, and the cell-body crawls through the wall. It has already been stated, in describing the processes of hemorrhage by diapedesis, that this transmigration was formerly supposed to take place through preformed gaps in the endothelium —so-called stomata or stigmata; but Arnold has shown that the cells always make their exit through the cement substance, which, under certain circumstances, is visibly broadened, in which case the walls of contiguous endothelial cells separate. It is probable that these minute changes are also responsible for the escape of albuminous *fluid* and the production of the inflammatory exudate,

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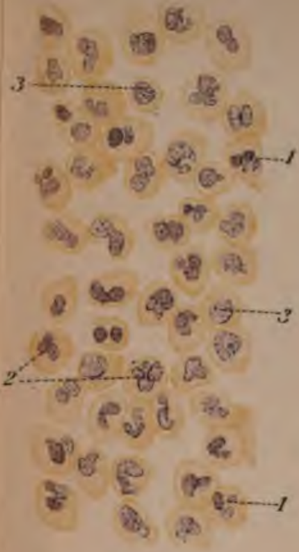

Fig.1

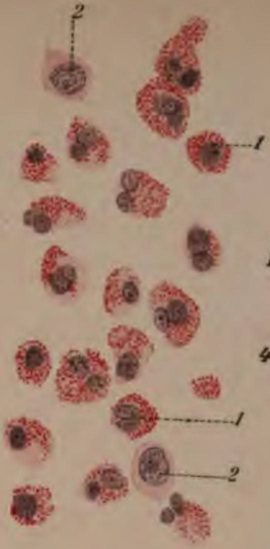

Fig.2

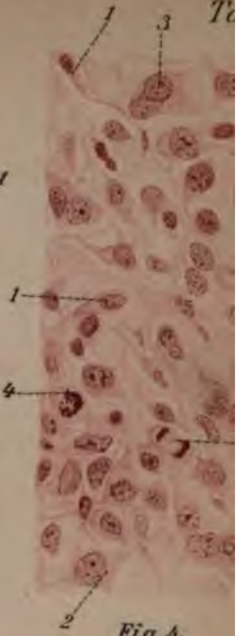

Fig.4.

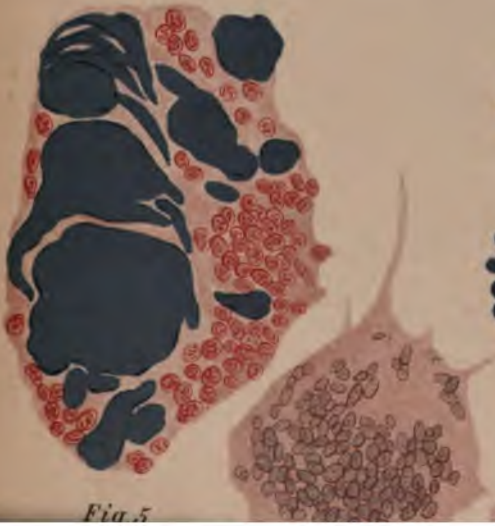

Fig.5

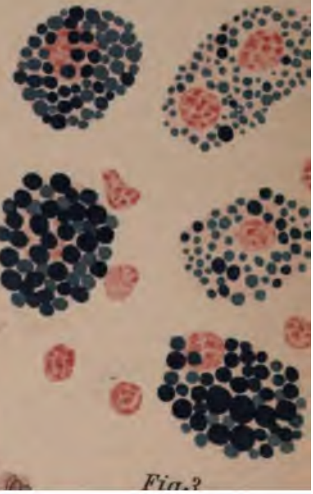

Fig.3

and that the escape of the leukocytes paves the way for the subsequent damage to the filtering membrane. If the velocity of the blood is still further diminished, the erythrocytes, which possess a still higher specific gravity, may also drift to the periphery, until the peripheral zone disappears altogether, and the entire lumen of the blood-vessel appears to be filled with masses of densely packed red and white blood-cells. As a result of increased pressure, red blood-cells may also escape or be forced through the walls; for the erythrocytes are incapable of taking any active part in this movement. When the process is extensive, the resulting serous or cellular exudate is mixed with blood from the start.

After their escape through the vessel-wall the leukocytes continue their active wanderings in the tissue, attach themselves to the preformed clefts and openings, and continue to throw out long, protoplasmic processes which always are nucleated and assume a great variety of bizarre forms; by this characteristic creeping movement they often cover a considerable distance in a very short time (Plate 30, Fig. 2). The shape and arrangement of the processes, the button-like swelling of one extremity, and the gradual passage of all the rest of the cell-body which contains the nucleus sufficiently indicate that the process does not consist in a simple carrying-off of the cells by the current, for the emigration of leukocytes is equally distinct in tissues which contain only a small amount of fluid.

Parts entirely devoid of blood-vessels may also become the scene of this emigration of leukocytes. The cornea has long been the accepted structure for the observation of this phenomenon. When the center of the membrane is converted into an inflammatory area by the introduction of a foreign body, by injury, or by infection, a triangular opacity rapidly develops with its base at the edge of the cornea and its apex directed toward the point of irritation. In this case the escape of leukocytes takes place from the marginal vessels of the cornea,—*i.e.*, the episcleral and conjunctival vessels,—and the cells wander through

PLATE 31.

Fig. 1.—**Accumulation of Leukocytes in Dilated Veins in Phlegmonous Inflammation of the Skin** (Hemat.-eosin. × 70.): 1, Fatty tissue; 2, dense accumulation of leukocytes; 3, masses of leukocytes in dilated veins.

Fig. 2.—**Emigration of Leukocytes in the Connective Tissue of a Heart Valve in Mycotic Endocarditis** (Hemat-eosin. × 625.): 1, Nuclei of fixed connective-tissue cells; 2, nuclei with pseudopods of wandering leukocytes; 3, sections of small remains of leukocytes.

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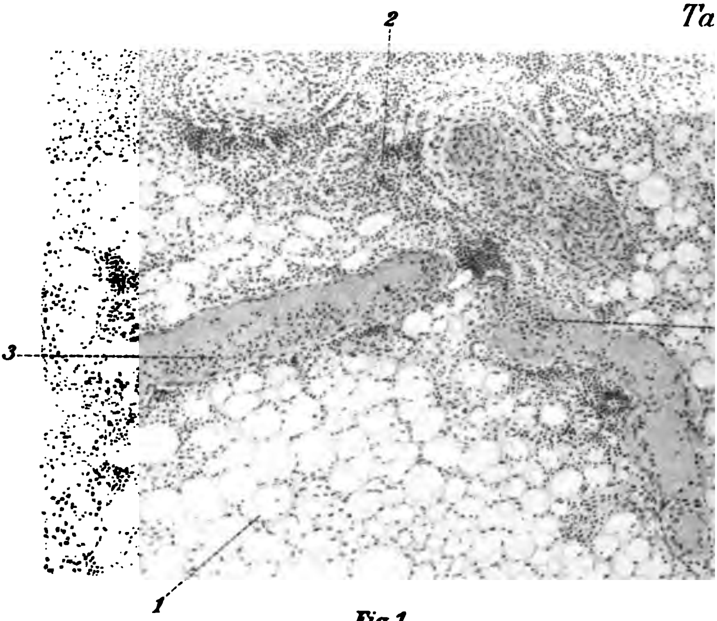
the tissue in exactly the same way as in cases of inflammation of vascular connective tissue, when they travel along the intervals between the vascular tracts. There is, therefore, no essential difference between inflammation of avascular and inflammation of vascular tissues; the former behave exactly like much enlarged interspaces in connective tissue.

To what is this active movement on the part of the leukocytes to be attributed, and why does it always drive them toward the point of irritation? The botanist Pfeffer was the first to show that some of the lower vegetable organisms—algæ as well as fission-fungi—are attracted by certain chemic substances, especially substances capable of furnishing nutriment to these lower forms of life. When a capillary tube filled with a substance of this kind is introduced into fluids containing some of these primitive, unicellular plants endowed with spontaneous movement, they gradually enter the tubes, their number being in direct proportion to the attractive power of the fluid. Pfeffer called this process *chemotaxis*, and it has been adopted for the explanation of the migration of leukocytes. Leber and Buchner were also able to demonstrate that the active substance is the albuminous material of the bodies of bacteria—bacterial proteins. Other decomposition-products of organized matter, as, for example, alkaline albuminates from muscle, liver, lungs, or kidney, also exert a marked chemotactic action on leukocytes. After the leukocytes have collected in large numbers in the tissue-spaces or in preformed



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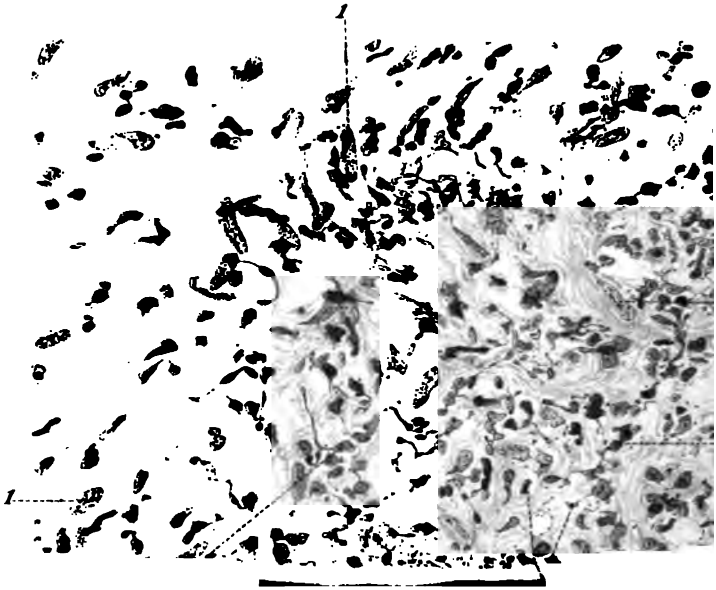

cavities, their bodies return to the circular shape and the nuclei resume their original polymorphous figures.

The protoplasmic bodies of leukocytes are divided into various forms, according to the granulations which they present: (1) The so-called *neutrophile leukocytes*, the protoplasm of which contains very minute granules that can be recognized only in the recent state. According to Ehrlich, they represent about 70 per cent. of all the migrating colorless blood-cells; (2) the *eosinophile leukocytes*, containing large granules which take a deep stain with the acid anilin dyes, especially eosin (Plate 30, Figs. 1, 2, and 3); (3) *basophile cells or mast-cells.* The large granules of these cells take the anilin dyes, such as methylene-blue and gentian-violet; (4) large *mononuclear leukocytes* with large protoplasmic bodies and circular nuclei, containing an abundance of chromatin; (5) *lymphocytes*, small spheric cells with a narrow protoplasm and a deeply staining nucleus, which fills almost the entire cell and in which the chromatin framework is recognized with difficulty.

The emigrated leukocytes are capable of multiplication even after they have escaped from the vessels, chiefly by direct division of nucleus and cell (amitosis). From the latter process must be distinguished the constriction which evidently explains the formation of the complicated forms of wandering leukocytes which are often observed, and in which small particles of cell-body, with or without a nucleus, are formed; the latter do not enlarge secondarily, and ultimately disintegrate and are destroyed (*cytodieresis*) (Marchand). After numerous leukocytes have thus escaped from the blood-vessels and wandered through the inflammatory area they may collect in such large numbers as to push aside the preformed constituents and form accumulations in spaces of their own production. They may have led also to solution of the tissue or of the fibrin formed during the inflammatory process, evidently by virtue of a fermentative action which the leukocytes exert on such substances. A true *histolysis* takes place (Leber). It is probable that this action is possible only

PLATE 32.

FIG. 1.—**Acute Purulent Keratitis** (Hemat.-eosin. × 200.): 1, Corneal lamellæ; 2, gaps in the cornea with accumulation of leukocytes; 3, massive accumulation of leukocytes.

FIG. 2.—**The Preceding Figure in Detail** (× 625): 1, Connective-tissue fibers of the cornea; 2, leukocytes; 3, granular detritus in areas of softening.

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on tissue that has previously undergone necrosis, and this necrosis may have been produced primarily by embolism or by the densely packed leukocytes themselves, by a sort of sequestration of the tissue. This ferment evidently has a peptonizing action on the albumin of the tissue, for the introduction of living and entirely sterile leukocytes into a test-tube is followed by liquefaction of the gelatin or of coagulated blood-serum. The histolysis is certainly not due [altogether—ED.] to the micro-organisms that often are present, for it takes place also when bacteria—*e.g.*, streptococci—do not exert the faintest peptonizing action on coagulated albuminous nutrient media. By virtue of this histolysis the closely packed leukocytes collect in large tissue clefts and cavities and an abscess is formed (Plate 6, Fig. 2).

The suppurative process may be superficial suppuration, taking place, for example, on the free surface of serous or mucous membranes. In the latter case it leads to so-called *purulent catarrh* (Plate 33, Fig. 2). In this condition the vessels in the mucosa and submucosa are distended to their fullest limit and contain an abundance of leukocytes, which escape through the vessel-walls in large numbers and traverse the entire thickness of the mucous membrane. Where the epithelium is composed of several layers, the latter are loosened and the lines of cement-substance broaden out. Through the latter the leukocytes escape and appear on the surface of the membrane along with desquamated and usually necrotic epithelial cells. When the epithelium is cylindric and consists of one layer only, it usually separates and is cast off in large masses, often more or less coherent. This may be accompanied

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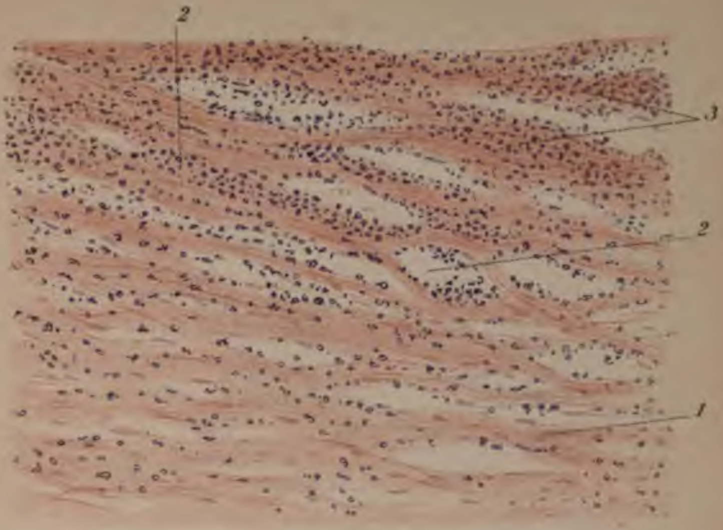

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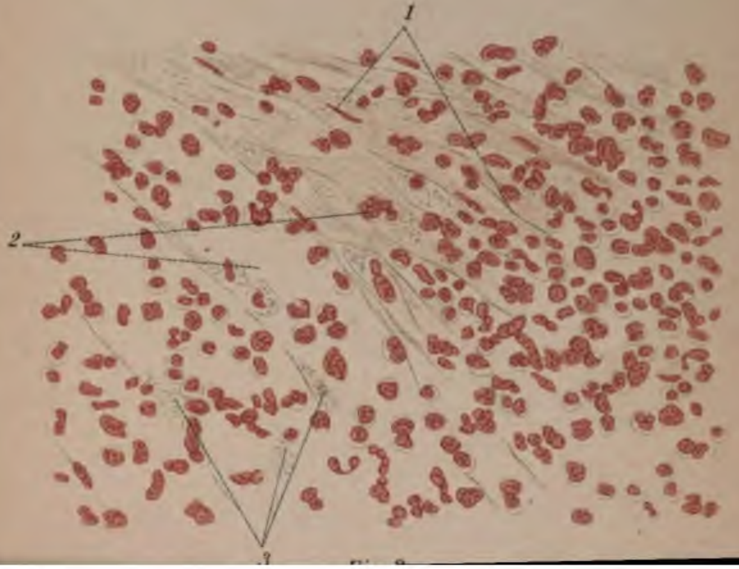

Fig. 2.

by increased production of mucus and the formation of innumerable goblet-cells. Necrotic epithelium, free masses of mucus, and desquamated goblet-cells mixed with numerous blood-corpuscles make up the purulent *catarrhal secretion.*

The ultimate fate of the leukocytes after they have escaped from blood-vessels and collected in the tissue is extremely variable. In cases of superficial suppuration they are simply cast off, or, in the case of suppuration on serous membranes, discharged into the serous cavities, where they cause an ever-increasing turbidity of the serum until the exudate becomes entirely purulent and forms a so-called *empyema.* Empyema, like the masses of leukocytes that collect in abscess-cavities, is capable of spontaneous absorption after the micro-organisms which caused the suppuration die or are destroyed by the phagocytic action of the leukocytes. The bodies of the pus-corpuscles at the same time undergo fatty degeneration and their nuclei break up into smaller and finally infinitely minute, dust-like particles, as in the case of karyorrhexis. In this way large collections of pus may be converted into a milky emulsion, which is capable of being absorbed through the lymph-vessels; a spontaneous cure is effected, and the remaining defect is filled by granulation-tissue which frequently is converted later into scar-tissue. Individual leukocytes in the tissue with other products of inflammation of their own accord may later travel back into the lymph-channels and be deposited in the sinuses of the lymph-glands, or they may at last find their way back by devious paths to the circulation and do duty again as leukocytes circulating in the blood-stream.

EXUDATION.

Before the escape of the white blood-cells an albuminous fluid in most cases filters into the inflamed area. The fluid in the tissues is increased in quantity, and the quality also differs greatly from that of normal fluid; for an inflammatory exudate is distinguished by its high per-

PLATE 33.

FIG. 1.—**"Parenchymatous Inflammation of the Liver;" Cloudy Swelling. Oxalic-acid Poisoning** (Hemat.-eosin. × 280.): 1, Central vein; 2, desquamated liver-cells that have been washed into the central vein; 3, swollen liver-cells with several nuclei; 4, budding of the nuclei of liver-cells.

FIG. 2.—**Purulent Catarrh in a Small Bronchus** (Hemat.-eosin. × 280.): 1, Muscular layer of the bronchial wall; 2, desquamated epithelial cells; 3, leukocytes.

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centage of albumin, which is almost equal to that of blood-serum. It has been said that these qualitative and quantitative changes are to be attributed to a primary change in the filtering membrane, and this leads us to the view that the first changes produced by the agent that is responsible for the inflammation is an injurious effect on the vessel-wall. The fluid exudate infiltrates the surrounding tissue, and, in obedience to physical laws, accumulates chiefly in dependent portions. In the case of connective tissue the meshes and clefts are forced apart and an *inflammatory edema* is produced, which is distinguished from passive edema by the greater percentage of albumin in the fluid and by the speedy appearance in it of emigrated white blood-vessels.

The best way to demonstrate the abundance of albuminous substances under the microscope is to dip the sections to be examined into boiling water a short time before they are hardened or cut into sections with the freezing microtome. In this way the inflammatory exudate is fixed *in situ*—*e. g.*, in the kidneys, within the capsule of Bowman, in the uriniferous tubules, or in the lungs, within the alveolar spaces surrounding the inflammatory foci.

On the external skin and in mucous membranes a marked infiltration of the individual layers also takes place. Sometimes the epithelial cells are swollen and filled with drops of exudate which crowd the nucleus against the cell-body. A more common effect in the case of skin or mucous membrane covered with stratified squamous epithelium is a solution of continuity, with the formation,

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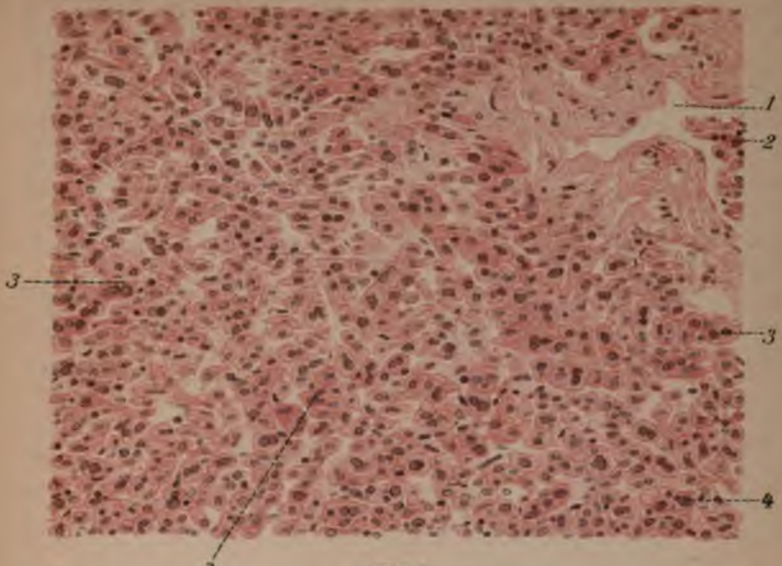

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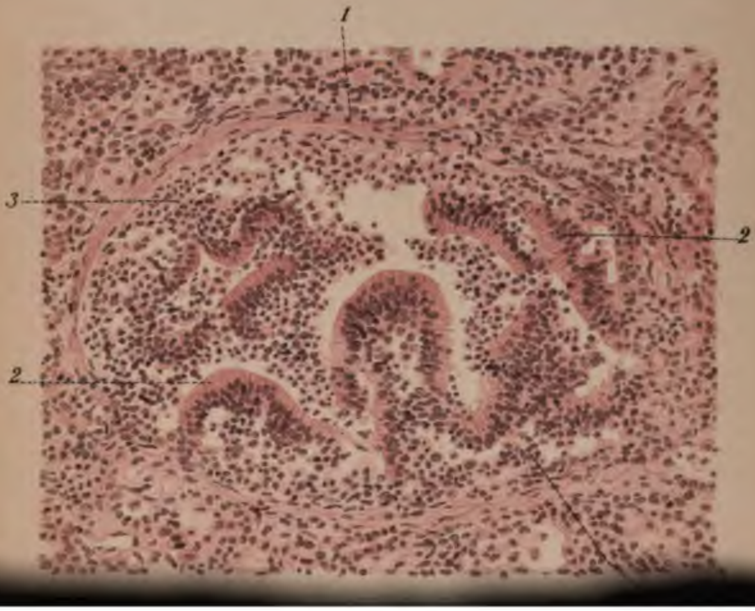

between the layers, of large, cystic cavities filled with exudate, terminating in the formation of a single blister or of a multilocular cavity divided by numerous septa in the form of a fan. On the external skin the vesicle forms usually between the so-called stratum granulosum and stratum spinosum—*i. e.*, the stratum corneum with the stratum lucidum, and the uppermost layer of epithelial cells, which still contains nuclei and in which the keratohyaline granules are deposited, form the roof, and the rete Malpighii the floor, of the vesicle. Sometimes, when the exudate accumulates slowly, as, for example, in the case of a small-pox pustule, the upper layer is not lifted off suddenly as a whole, but fluid accumulates gradually at the point of least resistance, and several smaller vesicles are formed close together, but divided by long-drawn-out epithelial cells that have escaped destruction. The fluid contained in the vesicles does not retain its serous character very long; almost as soon as it begins to accumulate leukocytes enter the cavity, passing through the cement-substance between the deeper layers of the stratum mucosum in large masses. The contents of the vesicle gradually become more and more turbid, and finally, just before the vesicle ruptures externally, are converted into pure pus. If the primary injury to the vascular wall has been intense, red blood-cells pass through with the leukocytes and also enter the cavities, so that the contents of the latter become dark and hemorrhagic (black small-pox) (compare *Atlas of Special Pathologic Histology*, Vol. II., Plate 115). In mucous membranes that are devoid of the stratum corneum the upper layer of the epithelium, of course, does not offer the same continued resistance to the collection of fluid; hence in the case of variolous pustules on the mucous membranes of the mouth and pharynx, for example, rupture takes place early and an open ulcer results.

In the case of the kidneys, the accumulation of serous exudate, particularly after it has been fixed in the manner described, is most successfully demonstrated within the glomeruli. As a rule, the exudation is accompanied by more or less extensive desquamation of epithelium from the glomerular coils; the cells are found in the capsular space pressed against its walls and often exhibit signs of retrogressive metamorphoses, especially fatty degeneration. In other portions of the kidney the vessels may pour out inflammatory exudate and cause pronounced inflammatory, edematous swelling of the parenchyma. The intervals between the uriniferous tubules widen out and contain everywhere an albuminous fluid which is more or less turbid from the presence of leukocytes.

When the inflammatory area is immediately contiguous to preformed body cavities, the inflammatory exudate is, of course, poured out into the cavities, and we often find large accumulations of inflammatory, serous fluid in the pericardium, pleura, peritoneum, etc.

As the fluid, which is strongly albuminous, contains an abundance of fibrinogen, it harbors within it the possibilities for the formation of fibrin-clots as soon as it comes in contact with a fibrin-ferment. This, in fact, occurs early, often, indeed, before the blood has left the vessels. In any portion of the inflammatory area fibrin-clots may develop in the vessels, which are distended to their utmost. At first they appear in the form of small, closely packed, stellate structures, or consist of a bundle of threads radiating in all directions (compare Plate 4, Fig. 1). The threads and small trabeculæ are seen to converge distinctly toward certain points, which usually represent leukocytes or the remains of leukocytes, blood-platelets, or desquamated endothelial cells—in short, some disintegration product of cellular material (*coagulation centers* of Hauser). In addition, these clots may be formed outside of the cells, in the connective-tissue clefts or between the cells of the tissues surrounding the blood-vessels. The fibrils, trabeculæ, and bundles of fibrin project out in all directions like crystals, and subsequently collect to form a dense network or assume a stratified arrangement; in these structures, also, especially during the initial stages, coagulation-centers with radiating fibers may be demonstrated; later on, as the excretion of fibrin becomes more copious, this arrangement, of course, disappears, and the fibrils cohere to form thicker, homogeneous trabeculæ. At this stage a more pronounced emigration of leukocytes usually takes place; for the fibrin naturally exerts a marked chemotactic attraction and presents a good pabulum for the leukocytes, which enter the meshes and continue to advance between the fibrils and trabeculæ, throwing out the characteristic pseudopods. Very frequently the tissue which is the seat of the exudate undergoes more or less extensive necrosis. The cells and nuclei perish, the chromatin exhibiting the usual rearrangements. This again liberates large quantities of fibrin-ferment, which causes an increase of the fibrinous exudate and inseparably unites the newly formed fibrin-masses with the reticular structures already formed. Thick, beam-like and knotted fibrinous clots are thus produced, and give the impression of a metamorphosis of the tissue itself into fibrin. This, however, is not the case; the coagulation progresses *pari passu* with the necrosis; the products of the latter are not observed, but the necrotic cells are at once replaced by fresh deposits of fibrin, so that the nuclei, which usually exhibit parietal hyperchromatosis and other karyorrhectic figures, are closely imprisoned in the spaces of the network of fibrin. The masses of fibrin, which at first are precipitated in the form of delicate threads, cohere and form thick, homogeneous masses, so-called *hyaline* or *canalized fibrin* (see Plate 16, Fig. 2). As this process of fibrin-formation is observed also in dying connective tissue, it has suggested the view that connective tissue may be directly converted into fibrin, a process which has been described by von Buhl as the formation of "desmoid fibrin," and by Wagner as "fibrinous metamorphosis of the connective tissue." Even at the present time some authorities (E. Neumann, Baumgarten) adhere to the possibility of a so-called "fibrinoid degeneration of connective tissue."

The epithelium of the serous membranes is usually in a fairly good state of preservation during the first stages of

PLATE 34.

Fig. 1.—**Inflammation of the Omentum in the Guinea-pig, Three Days After the Injection of Lycopodium Granules in Suspension** (Hemat.-eosin. × 625.): 1, Lycopodium granules in transverse section; 1′, the same, seen from above; 2, enlarged connective-tissue cells, fibroblasts; 3, fibroblasts in contact with the foreign bodies; 3′, multinuclear fibroblasts with large protoplasmic bodies; 4, nuclear proliferation in fibroblasts; 5, leukocytes.

Fig. 2.—**Recent Purulofibrinous Pleuritis** (Carmin; Weigert's fibrin stain. × 280.): 1, Pleural epithelium; 2, pleural connective tissue; 3, alveolar epithelium; 4, blood-vessels with proliferated endothelium; 5, fibrin in the marginal alveoli; 6, deposit of fibrinous exudate; 7, displaced epithelial cells within the fibrin; 8, leukocytes.

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swelling and loosening of the intercellular cement substance; here and there a few cells are cast off and defects appear. The cells in places appear to overlap one another. The subjacent connective tissue is loosened; the fibers are forced apart by the serous exudate; the blood-vessels are intensely injected; the endothelial cells are swollen, and show a remarkable tendency to project into the lumen—sometimes they may even present mitotic figures. The peripheral drift of the leukocytes within the blood-vessels is quite marked, and later a considerable emigration takes place. Red blood-cells also escape and are found free in the surrounding meshwork; the lymph clefts are likewise widened, and the cells which form their lining enlarged. It is at this point that the first stellate masses of fibrin are formed in the blood- and lymph-vessels. Leukocytes wander about between the connective-tissue fibers and through the clefts between the elastic fibers as far as immediately beneath the epithelium, or even make their way through openings between the cells and reach the surface. The first formation of fibrin can usually be traced above the epithelial cells. A coherent layer of fibrin, at first rather thin and fibrillar, evidently consisting of individual granules, makes its appearance and covers a considerable area of the membrane. In addition, however, delicate *particles* of fibrin may creep up underneath the somewhat

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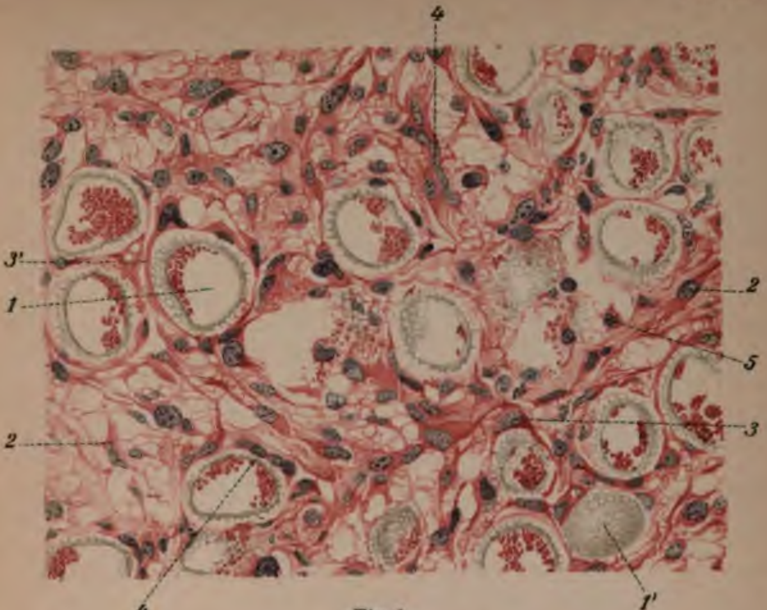

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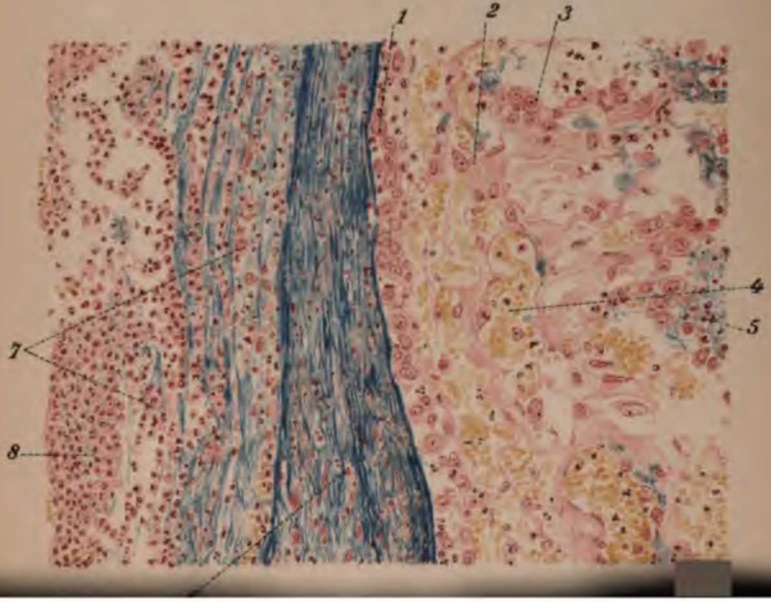

loosened epithelium or under the individual epithelial cells; sometimes, indeed, an extensive mass of thick fibrin in the form of trabeculæ or clumps accumulates immediately above the connective tissue and causes loosening of coherent or partially overlapping layers of epithelial cells, a fact that evidently is responsible for the view that connective tissue may be directly converted into fibrin. Later the masses of fibrin undergo a considerable increase, and in this tendency to form shapeless masses of hyaline trabeculæ is the more marked when the exudate is not turbid from the admixture of leukocytes; while in the case of purulofibrinous deposits, the fibrin usually persists for some time in the form of very delicate, parallel fibrils or of a close-meshed network, in the interstices of which the leukocytes accumulate.

The epithelium also undergoes degeneration, although at first proliferative phenomena may be observed for a time and mitotic figures may occur, followed by cell-division; but as the process continues, the cells are loosened from their connections, fat-droplets make their appearance in the cells, and the nuclei, after forming karyorrhectic figures, also fall a prey to progressive dissolution. Individual epithelial cells are always wrenched loose by the fibrin-threads, and may be forced a considerable distance outward; they can be distinctly recognized some time later by their cellular and nuclear forms. After the epithelium has disappeared, the fibrin, of course, lies directly upon the connective tissue. The latter may itself become the seat of fibrinous exudation, with the formation of small networks in the tissue clefts; later, as parts of the connective tissue undergo mortification, they may be replaced by newly formed fibrin, so that at certain stages of the process it is exceedingly difficult to distinguish the primary exudation fibrin from that which is formed secondarily in place of lost tissue. But even under these circumstances the theory of direct metamorphosis of connective tissue into fibrin is not tenable.

As everywhere else in the body, so also is primary fibrinous exudation, the fibrin represents only a temporary

PLATE 35.

FIG. 1.—**Diphtheria of the Uvula** (Carmin; Weigert's fibrin stain. × 40.): 1, Surviving squamous epithelium; 2, fibrin deposit; 3, fibrin within necrotic tissue; 4, necrotic superficial epithelium.

FIG. 2.—**A Part of the Above** (× 300.): 1, Swollen epithelium; 2, cystic cavities in the epithelium; 3, leukocytes; 4, fibrin; 5, nuclei of vanished epithelial cells in the fibrin.

PLATE 36.

FIG. 1.—**Croupous Pnuemonia, Gray Hepatization** (Alum-cochineal; Weigert's fibrin and elastin stain. × 280): 1, Alveolar septa with elastic fibers; 2, infiltrated perivascular connective tissue; 3, intra-alveolar fibrin; 4, intra-alveolar fibrin-bridges traversing Kohn's stigmata.

FIG. 2.—**Fibrinous Pericarditis in an Advanced Stage of Organization** (Picrocarmin. × 67.): 1, Epicardial connective tissue; 2, young granulation tissue; 3, newly formed blood-vessels; 4, islands of hyaline fibrin, completely surrounded by granulation tissue; 5, fibroblasts between the trabeculæ of fibrin.

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formation and must be removed again in one way or another; usually its removal is effected by disintegration of the fibrin-threads and their conversion into innumerable, minute fat-droplets suspended in a milky fluid and susceptible of absorption.

This process is most extensive in croupous pneumonia, the classic example of fibrinous inflammation. In this condition, also, the fibrin is formed by coagulation from an originally fluid medium—the inflammatory edema. In the early stages the appearance of coagulation-centers at the sites of the alveolar epithelial cells, which die in large numbers, can be most distinctly recognized, sending out pedunculated bundles of fibers into the alveolar lumen. (See *Atlas of Special Pathologic Histology,* Vol. I., Plate 36, Fig. 3.) At the same time large numbers of leukocytes invade the coagulating fluid and are caught in the close-meshed network. The cavities in the lung become practically filled with the exudate, more completely than in any other condition except after careful *artificial* injection, and, accordingly, the delicate stigma-like

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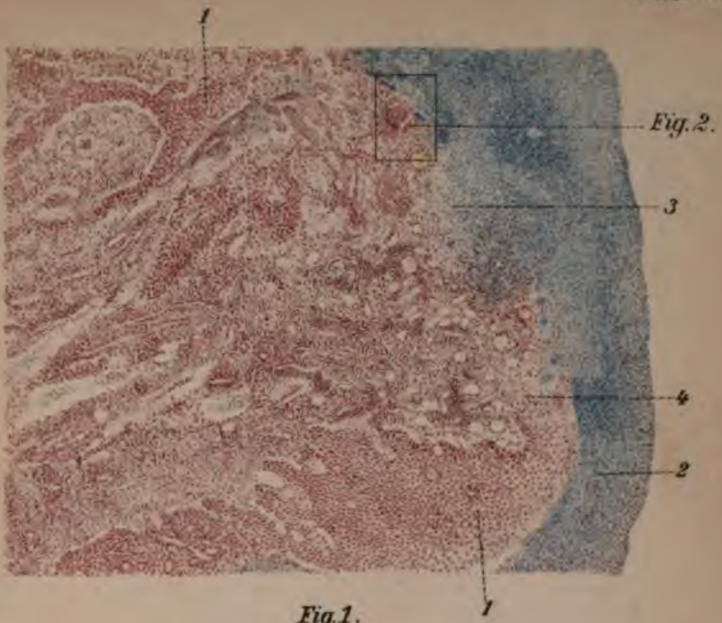

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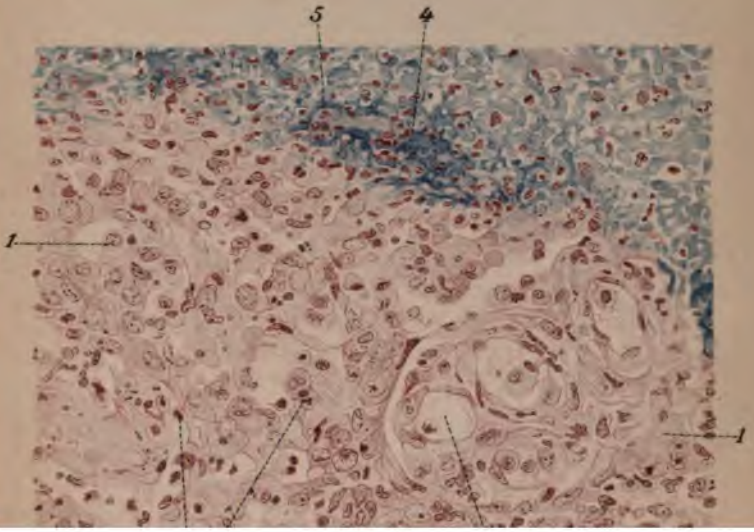

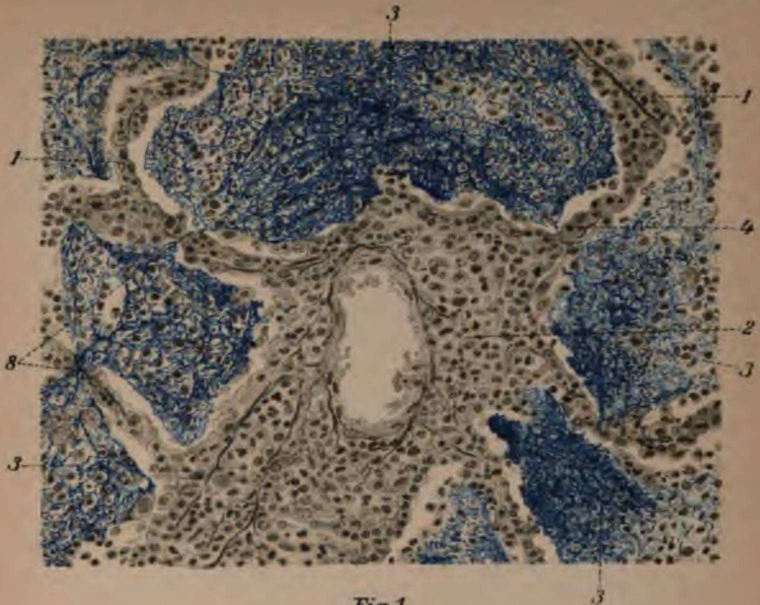

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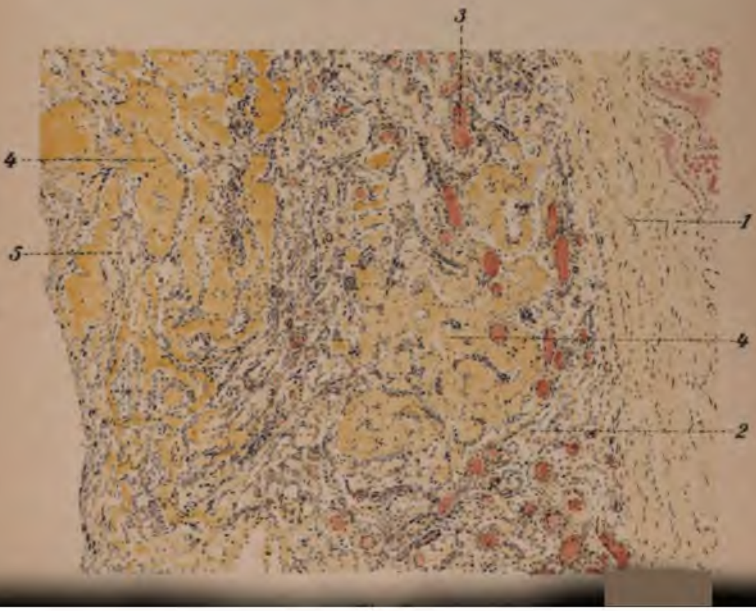

connections between the individual alveoli are traversed by fibrin-threads (Kohn's stigmata, Plate 36, Fig. 1). In places the fibrin-threads may collect to form thick trabeculæ. Later, during the stage of resolution, the fibrin, and along with it the imprisoned cells, breaks down into a turbid, viscous mass, and in this way a large quantity of exudate may be removed by absorption and expectoration. The quantity of exudate may be one kilogram or more; one-half of the mass probably consists of fibrin, while the other half consists of accumulated leukocytes, most of which have been formed during the disease.

But the fibrinous inflammatory exudate is not necessarily removed by simple absorption in every case; as we have seen in the healing of wounds, the *exudate may represent the forerunner of a newly formed connective tissue*—the fibrinous exudate may undergo organization. In the case of inflammation of serous membranes this process practically always occurs, at least to a certain extent. Spontaneous absorption [autolysis.—ED.] of fibrinous exudates in the pleura, peritoneum, or the pericardium, without further changes of any kind, is a great rarity. After the epithelium of the serous membrane has perished, young germinal tissue grows into the fibrin from the subjacent connective tissue, and causes its disappearance by active phagocytosis, while it is probable that resorption of broken-down fibrin also goes on at the same time. The germinal tissue consists of embryonal connective-tissue cells formed by mitosis (fibroblasts), mixed with small round-cells (polyblasts, Maximow) and a variable number of leukocytes, and is traversed by endothelial buds which grow out at the same time. As in the preëxisting connective tissue, some of the cells that have perished, as we have seen, are replaced by fibrin, and the invasion of the fibrin deposit by granulation-tissue does not take place everywhere at the same time; there results, at a certain stage of the process, a very intimate spatial commingling of proliferating tissue and fibrin. During the subsequent development of the granulation-tissue and the production of fibrous tissue by fibroblasts, which take place later single, isolated fibrin clumps may be completely imprisoned in places, and such islands of fibrin may be scattered here and there in the granulation tissue, so that the pathologic picture, unless the origin of the fibrin is carefully kept in view, is apt to lead the observer to assume a metamorphosis of connective tissue into fibrin. The imprisoned particles of fibrin gradually coalesce to form homogeneous, glistening trabeculæ, which represent the so-called hyaline fibrin, and the remains of which may be met during the later stages when all the surrounding space is occupied by fully formed fibrous tissue (Plate 36, Fig. 2). Ultimately this form of organization always results in the formation of a connective-tissue scar. When the process attacks opposite areas of serous membranes, it, of course, results in adhesions, which may be extensive and occupy a large portion of the serous surface, or circumscribed, like the span of a bridge (synechiæ). Connective-tissue thickening of the layers of the serous membrane may attain a high degree. In the case of the lung, when portions immediately below the pleura take part in the process, induration of the lung may result.

The fibrinous exudate which fills the lungs in croupous pneumonia is not completely eliminated in every case. The exudate may be replaced by ingrowing connective tissue, starting in the perivascular and peribronchial tissue and growing along the fibrin-threads from alveolus to alveolus like a running vine. The alveoli are thus prevented from collapsing, and their walls, after losing the epithelial lining, fuse with the invading connective tissue, resulting in permanent distention and solidification of the corresponding portion of the lung, which give it a solid consistence (chronic, fibrous pneumonia; *carnification.*) [Recently it has been shown that most cells contain digestive ferments which, on the death of the cells or tissue, may cause spontaneous solution of the latter—*autolysis.* Autolysis is regarded as playing an important rôle in the resolution of pneumonic and other exudates, the ferment being furnished principally by leukocytes.—*Ed.*].

A pathologic picture similar in every respect is observed in articular cavities after the formation of fibrinous exudate. The infiltration of the connective tissue with fibrin is usually complete and intimate, and after the fibrin has become organized, the newly formed connective tissue may secondarily undergo a hyaline change. In this way the so-called "*rice bodies*" are formed, which at first are united to the thickened synovial membrane, but later are liberated by the movements of the part.

Fibrinous inflammation of mucous membranes associated with necrosis of the tissue is designated **diphtheria.** Since it has been learned that the diphtheric inflammation which occurs so often in the form of an infectious disease, particularly in children, and attacks the pharynx and upper respiratory passages, is caused by a specific micro-organism, it would perhaps be better to reserve the terms diphtheria and diphtheric inflammation (diphtheritis) exclusively for the processes caused by Löffler's diphtheria bacillus, and to call the inflammations of the mucous membrane which occur elsewhere in the body and are attended by exactly the same anatomic changes "diphtheroid" or necrotizing inflammation of mucous membranes. For it is known that the diphtheria bacillus is by no means the only cause of this process, which may be due to other bacteria (streptococcic, typhoidal, dysenteric infections), as well as to any one of a number of chemic agents (corrosive sublimate, ammonia, cantharides, mineral acids), to burns and exposure to severe cold, and finally to ischemia or infarction. The common feature of all these processes, which differ greatly among themselves, is the primary occurrence of necrosis of tissue, which in one case is brought about by the toxic metabolic products of the diphtheria bacillus; in other cases, for example in uremia, by the ammonia excreted in the intestinal mucous membrane, or, for example, in embolism of a mesenteric artery, by ischemia. The inflammatory action of the mucous membrane to the necrosis is identical, whatever may be the cause of the necrosis, and consists in the deposition of a firmly coagulating exudate which originally is derived from the plasma that escapes from the injured blood-vessels. As in this case the tissue-necrosis was present from the beginning and the formation of fibrin-ferment is, therefore, abundant and extends over a large area, exudation-fibrin is formed not only on the surface of the affected mucous membrane, but also within its tissue, particularly in places where parts of the tissue have been destroyed; the fibrinous deposit accordingly becomes united so intimately with the tissue that it is more difficult in this condition than in any other to disprove the theory that the tissues of mucous membranes may be directly converted into fibrin. At the first glance it appears to be absolutely impossible, in pharyngeal diphtheria, for example (Plate 35, Figs. 1 and 2), to distinguish between the fibrinous deposit and the fibrin which has taken the place of lost epithelium. At the edges of the fibrin the epithelium exhibits all the stages of karyorrhexis and karyolysis; the orderly arrangement of the cell-layers is disturbed, the cells are loosened from their connections, and in places large and small cysts filled with fluid are formed, leukocytes in large numbers invade the interstices between the epithelial cells, and here and there a mitotic figure may be demonstrated, testifying to an attempt at reactive proliferation. Most of the nuclei, however, exhibit karyorrhectic figures in one or the other of their stages. In the zones immediately above (Plate 35, Fig. 2) the spaces between the nuclei are not occupied by cells, but exclusively by thick trabeculæ of fibrin, connected with one another in the form of a network. The latter frequently present a glistening, hyaline appearance (Plate 16, Fig. 2), so that the nuclei appear to be dissolved out of the fibrin and to be lying free in the canal-like spaces. At the edge of the necrotic area and of the secondary deposit of fibrin the leukocytes usually accumulate in large numbers and form a kind of line of demarcation from the normal tissue. The tissues of the mucous membrane, after they have become infiltrated with fibrin and lost their vitality, are, of course, cast off, and the *diphtheric* or *"diphtheroid" ulcer* is formed. The lost tissue is replaced by regeneration of the surrounding epithelium, and, when the ulcer is deep, by that of the subepithelial connective tissue as well (see above, Pathologic Organization). If only a fibrinous membrane consisting of coagulated masses of exudate is deposited on the mucous membrane, and the necrosis involves only the superficial layers, the process is described as *croup.* But croupous and diphtheric or diphtheroid necrotic processes are frequently associated; for while the exudate may project above the level of the croupous membrane and by coagulation form a croupous membrane, the necrosis may continue in the deeper layers and ultimately form a diphtheric membrane, so that the two processes cannot be distinguished from one another.

A fibrinous exudate is frequently deposited in lymph-glands with or without a necrotizing inflammation of neighboring mucous membranes; the deposit takes place chiefly in the lymph-sinuses, and is probably in every case to be attributed to the effect of the same noxious agent, which has been brought in by the lymph-stream. Thus, for example, the maxillary and cervical, as well as the tracheal, lymph-glands are enlarged in diphtheria of the pharynx and of the upper air-passages. A process which is anatomically quite similar takes place in the follicles of the intestine and in the mesenteric lymph-glands in the necrosis of *typhoid fever.* Extensive networks of fibrin with simultaneous necrosis of the lymphocytes and of the endothelial cells in the lymph-sinuses are observed also in the necrosis of *bubonic plague* in the lymph-glands of the groin (Dürck).

Productive inflammation is characterized by a chronic course and is attended from the beginning chiefly by a new formation of germinal tissue, which in every instance is ultimately converted into connective tissue. It has already been seen that in parenchymatous tissues proliferative phenomena attending inflammation are always of a transitory nature, and are soon replaced by degenerative changes. The histologic processes of productive inflammation, which always take place in the connective tissue of blood-vessels, do not differ in any

PLATE 37.

FIG. 1.—**Tubercle from the Lung with Distinct Reticulum** (Hemat.-eosin; orcein. × 320.): 1, Elastic fibers from the alveolar wall; 2, giant-cells; 3, pseudopods of the latter, communicating with one another.

FIG. 2.—**Diffuse Tuberculous Granulation Tissue from the Kidney** (Hemat.-orange. × 280.): 1, Nuclei of epithelioid cells; 2, giant-cells; 3, fibrinoid substance between the cells.

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way from the processes that we have already studied in detail in connection with pathologic organization.

SPECIFIC INFLAMMATIONS.

Infectious Granulomata.

The term infectious granuloma (granulation tumor) is applied to the specific form of inflammation which is due to the invasion of the body by certain definite infectious micro-organisms. As these inflammatory products appear practically always in the form of a sharply circumscribed new formation of tissue, they were included with true tumors in a common group of progressive processes; but, as we shall see when we come to discuss tumors more in detail, there is always an essential difference; the formation in each case is fundamentally different, and only a superficial inspection, without any knowledge of the underlying causes, could ever have led to this view. The reaction of the tissue varies according to the nature and peculiarities of the invading parasitic germ; generally speaking, the subsequent course is typical for each micro-organism, and in many cases it is possible to infer the species of infectious invader from the histologic appearance of the tissue proliferation.

Granulomatous growths usually continue to enlarge so long as the vegetation of the microparasite lasts, and when the latter perishes in the organism, secondary retrogressive metamorphosis may take in the granulomata.

Granulomata exhibit a fundamental difference from *true* tumors in their manner of spreading in the organism.

Tab.37.

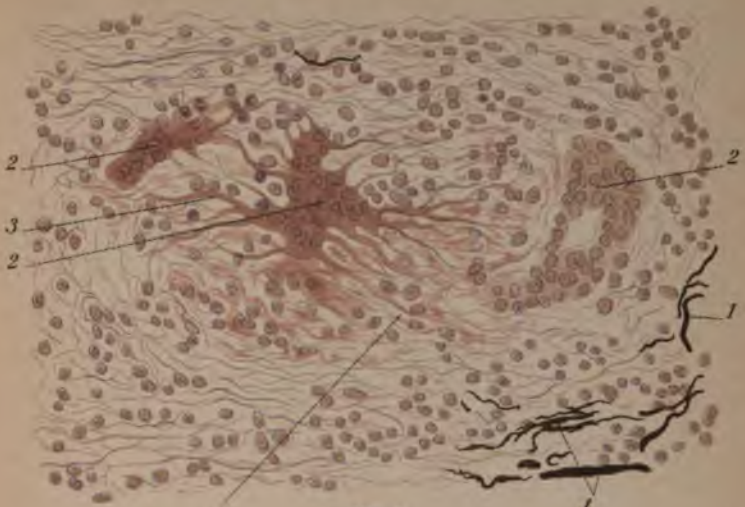
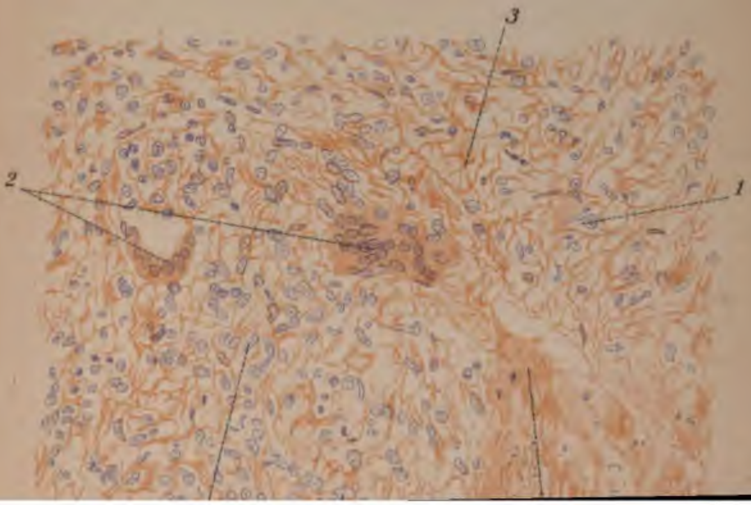


Fig.1.



The spread of infectious granulomata in the organism from the point of invasion, where they in many cases, although not always, produce the first inflammatory phenomena, the so-called *primary lesion*, always takes place by the transport of the parasitic germs in the blood- or lymph-stream, or in some other way, to distant portions of the body, where they set up an inflammation precisely similar to that which takes place at the site of the primary invasion. True neoplasms, on the other hand, always form metastases by the removal of parts of the mother tumor to other organs or parts of organs. These particles are arrested and implanted in the tissue, and from these implanted tumor-particles, which possess the faculty of proliferation, other tumors in every respect similar are produced.

Many of the infectious granulomata lead to the formation of nodules built up of cells, which Virchow designated "tubercula." These diseases, therefore, are all called "tubercle diseases." [In American literature the term tubercle is applied only to lesions caused by the tubercle bacillus.—Ed.] These tubercles are most frequently due to the activity of a micro-organism which, because it possesses in a high degree this property of producing tubercles in human and animal bodies, has been called the "tubercle fungus."[1] In addition there are other parasitic as well as non-parasitic causes that may lead to the formation of tubercles [*i.e.*, nodules.—Ed.] within the body; thus it is sufficient, in order to produce them, to incorporate small foreign bodies in uniform suspension, as, for example, ground wheat, small particles of hair, or cuttings of silk thread. There is another class of diseases, which includes syphilis, glanders, lep-

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[1] As the cause of tuberculosis, according to recent investigations, should not be included among the monomorphous bacteria and does not represent a single bacillus, but belongs rather to the group of streptothrices,—*i.e.*, pleomorphous bacteria,—the name "tubercle bacillus," which has long been current, has been discarded in this work, and, instead, the term "tubercle fungus" will be used. [According to the law of priority actinomyces should be used rather than streptothrix.—Ed.]

PLATE 38.

FIG. 1.—**Exudative Tuberculous, Cheesy Hepatization of the Lung** (Alum-cochineal; Weigert's fibrin, and elastic connective-tissue stain. × 280.): 1, Alveolar walls in a perfect state of preservation with elastic fibers; 2, caseous exudate with disintegrated nuclei of leukocytes and scattered alveolar epithelial cells; 3, fibrinous exudate; 4, fibrinous interalveolar bridge.

FIG. 2.—**Caseation in a Tubercle from the Pia Mater** (Hemat.-eosin. × 645.): 1, Epithelioid cells; 2, epithelioid cells engaged in migration, with long-drawn-out nuclei; 3, round-cells; 4, disintegrated nuclei within epithelioid cells; 5, free nuclear débris; 6, masses of tissue in which caseation is complete and the nuclei have all disappeared.

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rosy, and actinomycosis, in which the inflammatory reaction of the tissue after it has been damaged by these parasitic agents manifests itself in nodular new growths. It is undeniable, however, that the eruptions of nodules due to the tubercle fungus exhibit such pregnant peculiarities, evidently due to the peculiar mode of action of the etiologic agent, that they are thereby distinguished from all other tubercular [nodular.—ED.] diseases.

1. Tuberculosis.

The morbid phenomena produced by the entrance of the tubercle fungus into the organism and the manifestations of its activities are designed "tuberculosis." The disease most frequently manifests itself in the body by the production of cell-nodules and is, therefore, a "tubercle disease;" but it may also manifest itself in other forms, especially as a diffuse granulation tissue and in the form of an exudative inflammation. According to the present state of our knowledge, the presence of tubercles is not the only diagnostic criterion of tuberculosis; for the term tuberculous is applied to all those changes in the body which are produced by the tubercle fungus.

The commonest product of the tubercle fungus is the *tuberculous nodules*, or simple tubercle. It always repre-

Tab. 38.

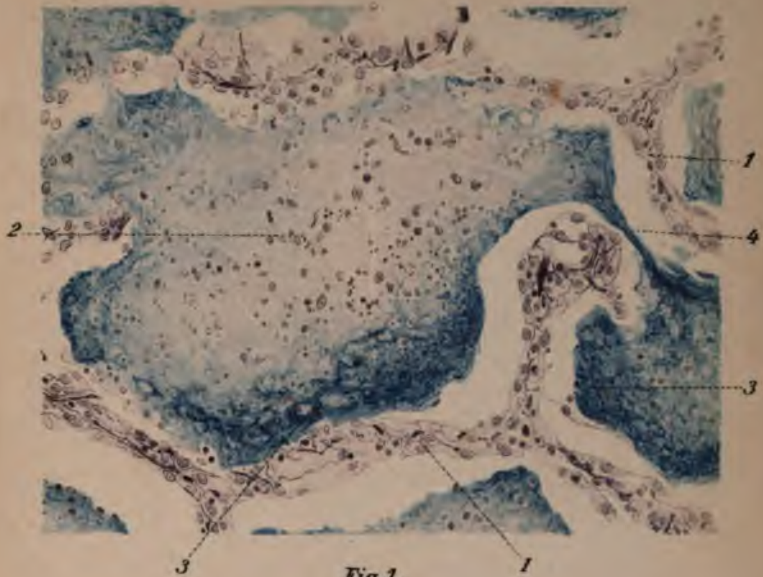
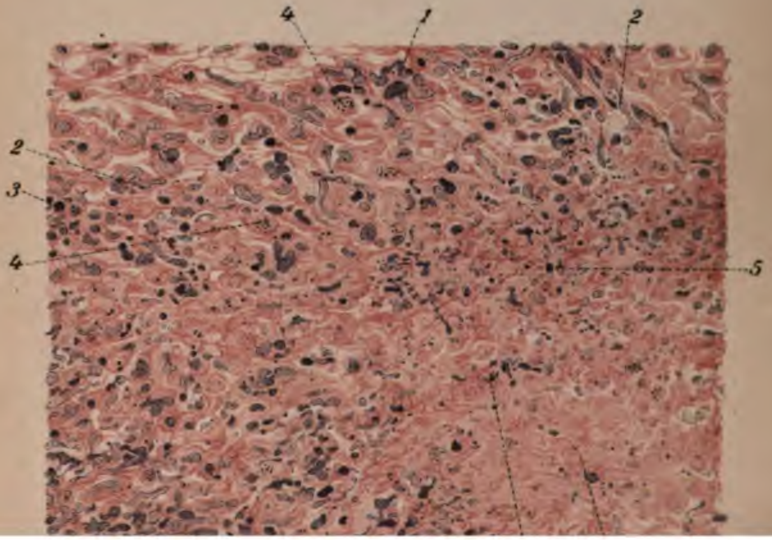


Fig. 1.



sents a new growth in the affected tissue; and it consists not of a collection of newly collected cells, but rather—at least during the initial stages—of derivatives of fixed tissue-cells. The tubercle is produced from the cells of the organ at the site of the injury. The exact nature of the action of the fungus has not as yet been clearly explained, and opinions concerning it differ. Weigert believes that the proliferation is secondary and follows injuries to cells and intercellular substance, which represent the primary effects of the tubercle fungus. In other words, the condition is a perfect analogue of simple inflammation, in which we also have a primary injurious effect on certain portions of organs, especially degenerative processes in the vessel-walls, as the first result of the action of the irritant that is responsible for the inflammation, while all subsequent exudative and cellular processes are due secondarily to this injury.

In the formation of the tubercle the proliferative inflammatory processes play the most prominent rôle. The first result of the invasion of the tissue by tubercle fungi appears in the swelling and mitotic division of the preexisting fixed tissue-cells. These elements usually group themselves in the form of a circle or of a hollow sphere about the invading tubercle fungi, their protoplasm swells, and the cells thus form a dense mass. Owing to this behavior Virchow called these cells "epithelioid" cells, because they are connected with one another like epithelial cells. Later the expression "epithelioid cells" was often used erroneously and was applied to special forms of cells, to emphasize the abundance of their protoplasm. This conception is, however, entirely erroneous; for a connective-tissue cell may also have a very large body, while, on the other hand, epithelial cells when in close proximity to one another assume a great variety of forms and sometimes possess only a very small quantity of protoplasm. The distinguishing feature, therefore, is not the shape of the cells, but their mutual arrangement. These epithelioid cells in most cases are probably produced by the proliferation of connective-tissue and endothelial cells, and are therefore in every respect comparable to the fibroblasts of simple inflammation.

Many authors even now adopt the view that under the influence of tubercle fungi any cell in the human body may proliferate and produce epithelioid cells, thus becoming the corner-stone for a young tubercle. It is quite true that the first eruption of tuberculous granulomata in all parenchymatous organs is attended by a fairly active proliferation of the fixed parenchyma cells, manifesting itself chiefly in a more abundant mitotic division of these cells. Thus, in the liver, for example, after the injection of tubercle fungi into the portal vein, karyokinectic figures are seen in the cells as well as in the epithelium of the bile-ducts at the places which correspond to later eruptions of cell-nodules, and which immediately surround the tubercle fungi that have lodged in the capillaries. Again, in the kidneys, a similar proliferative activity is observed in the epithelium of the uriniferous tubules at a very early stage of the process after an injection of tubercle fungi. But the finding of mitotic figures in these cells is far from proving that the cells themselves have been converted into the elements of a tubercle, and, as Hansemann has pointed out, the assumption is not tenable on theoretic grounds in view of the generally accepted law of the specificity of the cell (*omnis cellula e cellula ejusdem generis*). We shall see later that the cells of tubercles may occasionally appear in the character of connective-tissue builders, but it is incompatible with our present views in regard to the differentiation of cells to assume that a cell which formerly had been an epithelial cell and formed part of a glandular organ or a mucous membrane, or one of its descendants, can ever produce connective tissue; even through the mediation of tubercle-formation so complete a change in the character of a cell is absolutely inconceivable. It is needless to say, however, that proliferative processes may be set up in all the parenchyma cells of the body if specific inflammatory products, such as tubercles, establish themselves in the surrounding tissue. But *these proliferative* processes are only transitory, and are usually the forerunners of degenerative conditions, just as we found ourselves forced to deny the occurrence of true parenchymatous inflammation in the sense of a permanent cellular proliferation in parenchymatous organs, without being able to deny the occurrence of momentary proliferative conditions as the expression of an early stage of the lesion. An eruption of tubercles is often observed in the immediate neighborhood of epithelial cells; the latter, by multiplication, undergo a considerable increase both in number and volume, without being themselves included within the area occupied by the tuberculous granuloma. For example, in tuberculosis of the mucous membrane of the larynx the epithelium may undergo considerable thickening, and metaplasia of the membrane may even take place, so that stratified squamous epithelium is produced in places which normally are covered only by cylindric epithelium (*pachydermia laryngis*). A similar behavior is observed in the ependyma of the ventricles of the brain when tubercles form beneath them. The cells undergo proliferation, but they are not themselves converted into tubercle cells. Since, therefore, the most important source of supply for the growing tubercle is represented by the fixed connective-tissue cells and the endothelial cells, the epithelioid cells are in every way comparable to the fibroblasts in simple inflammation. The only peculiarity about their use in building the tubercle is their radiating arrangement.

When the young, growing tubercle, consisting of epithelioid cells, is found in the immediate neighborhood of blood-vessels, the latter are almost always occluded, either by compression from the expansive growth of the granuloma or by active ingrowing of the latter into the vessel-wall, with partial utilization of its cells for the tubercle. The endothelial cells may undergo considerable swelling and sometimes even exhibit active mitotic division.

Sometimes at an early stage of the tuberculous growth these epithelioid cells are converted into *giant-cells*. The formation of these structures may in general be regarded as the expression of a diminished vital activity. We dis-

PLATE 39.

Reticulated Tubercle from the Diaphragmatic Peritoneum (× 150.): 1, Epithelioid cells; 2, large giant-cell with cheesy cell-body; 3, zone of caseation; 4, abundantly developed reticulum; 5, embryonal, concentrically striated connective tissue in the neighborhood.

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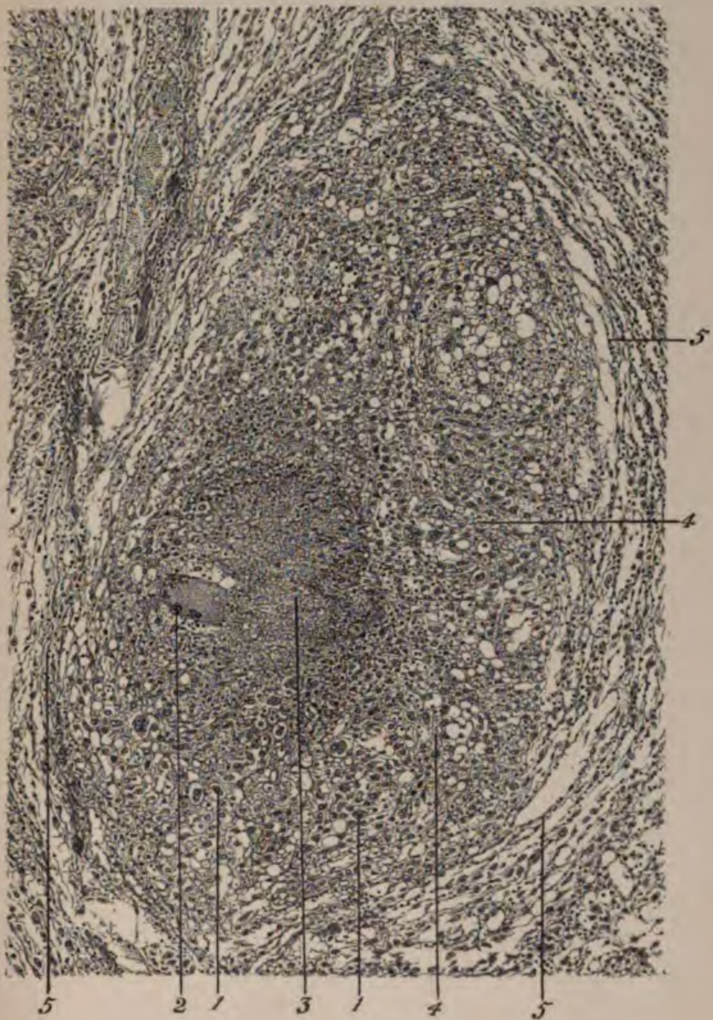
tinguish three forms of giant-cells in the tubercle: (1) The proliferation giant-cell, formed by rapid nuclear division in the same cell, while the growth of the body fails to keep pace. The division is very often amitotic—that is, effected by direct division or fragmentation. Sometimes the cell-body exhibits local necrosis or caseation, while the proliferative processes still go on in the nuclei (Weigert). (2) A second form of giant-cells undoubtedly is produced by the fusion of neighboring cells (conglutination giant-cell) although from the fact that many of the cells are multinuclear it is probable that a secondary multiplication of the nuclei takes place in the body-protoplasm, which owes its size to the confluence of several individuals. (3) Finally, the picture of a giant-cell may be simulated by transverse sections of a hyaline thrombus in a blood-vessel with enlarged or confluent endothelial cells. The third form, it is needless to say, is not a true giant-cell formation, and is distinguished, as a rule, by its regular, circular form and externally smooth, well-defined contours; but its true origin can be recognized only by examining a large number of serial sections. It is certain at least that this form of giant-cells has nothing in common with the genuine tuberculous giant-cell of Langerhans.

When in this way, by proliferation of the cell-group which has felt the first effect of the fungus, the tubercle has attained a certain size and is usually just visible to the naked eye, other elements gather in its periphery. Small round-cells after the type of leukocytes accumulate, at first only in or around the peripheral zone, and contribute to the enlargement of the nodule; before long, however, these round-cells actively invade the central

Tab. 39.



portions of the tubercle. This admixture of round-cells is extremely variable and by no means equally pronounced in all tubercles. It may be so marked as to force the endothelial cells apart and later practically cause their disappearance, or it may be altogether absent for a long time, even after the central portions of the tubercle have become the seat of retrograde metamorphosis. These round-cells are unquestionably derived from the blood-vessels in the neighborhood which have been altered by the tuberculous eruption; they are in a general way comparable to the small-cell infiltration in simple inflammation, composed of the so-called "polyblasts" (Maximow) or "leukocytoids" (Marchand). During the later stages polymorphonuclear leukocytes also appear in addition to the mononuclear forms; they may emigrate in enormous numbers and collect at the periphery of the tubercle, so that the latter appears to be imbedded in an exudate of pus-cells.

Other exudative phenomena are occasionally prominent in the formation of tuberculous granuloma; thus, for example, a variable quantity of fibrin, evidently the result of profound injury to the vessels and consequent exudation, may be deposited in the central as well as in the peripheral portions of the tubercle. The quantity of fibrin is quite inconstant, and great variations take place within the same organ, from entire absence to deposition of an abundant network. At all events, the variable degree in which coagulable inflammatory exudate takes part in the process indicates that the exudate does not represent an integral constituent of the tubercle; its appearance depends on secondary factors—possibly the degree of virulence of the tubercle fungus.

Every tubercle, furthermore, possesses a delicate fibrillar framework, the development of which also varies and which is known as the *reticulum*, as it is usually spread out in the form of a delicate intercellular substance between the epithelioid and giant-cells. Formerly it was often regarded as an artefact, produced by the action of the preserving fluid on the succulent cells of the young tubercle; but numerous examinations have shown clearly that the reticulum occurs independently of the kind of preserving fluid used, and is a well-marked and essential constituent of the tubercle. Its origin is probably due to various causes. Part of it is undoubtedly derived from the remains of the fibrous ground-substance of the tissue of the organ in which the tubercle has formed, and this portion accordingly will be of a variable quantity, depending on the abundance of fibrous substance in the affected organ. In serous membranes, for example, the reticulum in a growing tubercle is beautifully seen (Plate 39). The fibers of the stream are forced apart by the proliferating elements; they become drawn out and attenuated; the reticular substance may accordingly be delicate, and probably is entirely destroyed in many places. Another part of the so-called reticulum no doubt owes its existence to newly formed fibers which represent processes of epithelioid and giant-cells. The latter particularly often exhibit a large number of interlacing, protoplasmic processes, like spider's feet, which unite with one another and with those of the neighboring epithelioid cells to form a continuous network (Plate 27, Fig. 2). Finally, a fibrous reticulum may owe its origin to a newly formed, coagulable intercellular substance between the elements of the tubercle. This in most cases probably consists of so-called fibrinoid substance which, as will be mentioned presently, bears certain relations to the retrograde metamorphoses which take place within the tubercle, and may be spread out between its cells in the form of a delicate fibrillar network.

It follows, therefore, that in every organ the tubercle presents a new formation developing from the proliferation of certain preëxisting tissue-cells. But tubercles may also be produced outside of organs, particularly in fibrinous exudates. Here they appear as islands or nests of cells scattered here and there and surrounded on all sides by fibrin. It is these tubercles, which are produced without any connection with fixed organ cells, that have *always* been utilized by the adherents and defenders of the doctrine that the tubercle is exclusively formed from emigrated leukocytes as a proof of the correctness of their views, on the ground that both the cells in the fibrin deposits on serous and articular membranes can get there in no other way than by emigration, and that these tubercles are, nevertheless, built up of "epithelial" cells and giant-cells, just like tubercles that grow in the interior of organs and are connected with the tissues of those organs. It is true that these isolated tubercles can be formed only from "wandering cells"—that is, cells endowed with the power of spontaneous locomotion; but, as we have seen in the description of simple inflammatory granulation-tissue, the descendants of the fixed connective-tissue cells and of the endothelial cells, the fibroblasts, are endowed with a well-marked power of movement and are quite able, by their own efforts, to make their way into the meshes of fibrin—in fact, this is the rule in the healing of a wound whenever the defect is primarily filled with fibrin. The fibroblasts traverse the fibrin, which is partially consumed by them during their progress and exerts a positive chemotactic action, not only on the leukocytes, but also on the fibroblasts themselves and on the vascular buds. It is no wonder, then, that a tubercle may be formed in this way whenever the causal micro-organisms are present in a fibrinous membrane; fibroblasts advance as far as the micro-organisms and form a wall of epithelioid cells around them. At the same time lymphocytes and leukocytes in variable quantities may invade the tissue and contribute to the enlargement of the tubercle.

The tubercle, however, is not the only manifestation of inflammatory reaction in a tissue which becomes invaded by tubercle fungi. Instead of circumscribed nodules, a *diffuse granulation-tissue* may be produced, which is built up in the same way as the granulation-tissue in simple inflammation and is distinguishable from the latter only by the presence of the specific organisms and by a tendency to undergo retrograde metamorphoses. This reaction is obviously found when large quantities of tubercle fungi exert their influence at the same time over a large extent of tissue, as, for example, in the kidney, when large quantities of tubercle fungi are excreted, in the ureters, in the mucous membrane of the uterus, and sometimes, especially in animals (cattle), on serous membranes in the presence of an abundant exudate containing tubercle fungi. The principal difference between this newly formed granulation-tissue and the tubercle is the presence of newly formed blood-vessels, which are never found in a circumscribed tubercle. Subsequently tubercles may develop within the granulation-tissue and are then sharply marked off from the surrounding tissue by a dense, peripheral wall of round-cells.

Finally, the tubercle fungus is capable of producing a purely *exudative superficial inflammation*, in which the inflammatory exudate may present all the variations from simple serous to fibrinous or purulent material. Thus, for example, there are varieties of tuberculous leptomeningitis in which the tissue reaction consists solely [or largely.—Ed.] in a copious accumulation of simple purulent or purulofibrinous exudate. The lung in particular may be from the beginning the scene of a simple exudative tuberculous inflammation, which, accordingly, during its first stage, differs in nowise from that of an ordinary exudative inflammation, as, for example, a croupous pneumonia. The alveolar septa remain entirely intact, are not thickened, and at most suffer some proliferation of their epithelial lining. In the interior of the alveolar lumens, however, an exudation accompanied by fibrin takes place, which is associated with the emigration of lymphocytes and leukocytes. The exudate, however, is not dissolved or organized in the usual way; its specific, tuberculous character asserts itself, and it undergoes secondarily a typical caseous necrosis. But neither a circumscribed nor a diffuse granulation is ever formed at any stage of the process (Plate 38, Fig. 1). In this way large sections of the lung may be attacked by exudative processes which later, by the appearance of caseous necrosis, lead to the development of so-called *cheesy hepatization.*

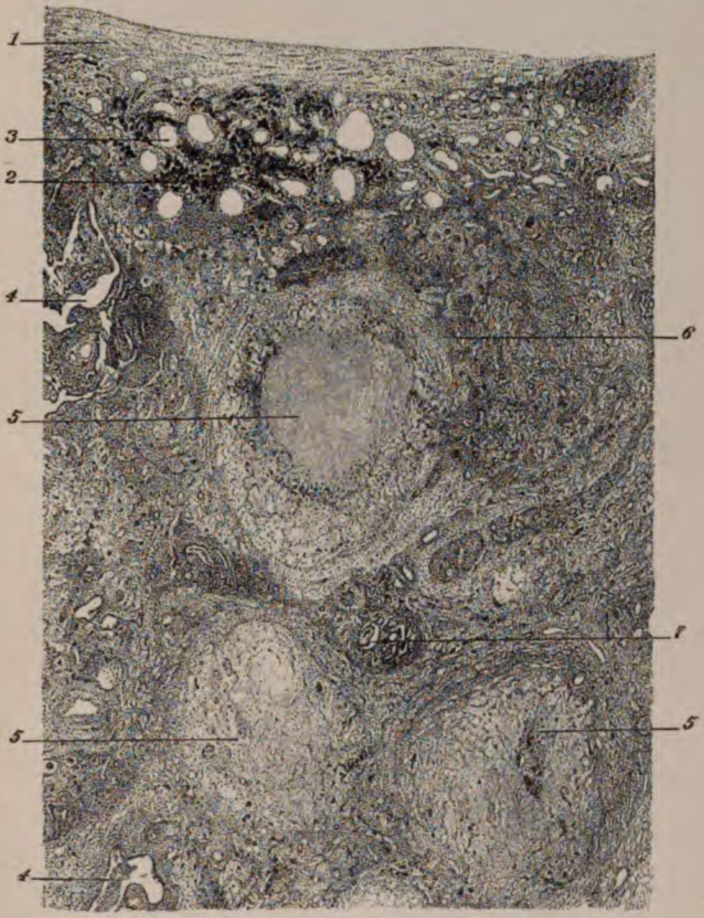
All tuberculous structures, circumscribed tubercles, diffuse granulation-tissue, as well as the purely exudative formations, harbor within them the germ. In a short time they fall prey to the peculiar form of necrosis designated *caseation—i.e.*, the final result of which is a dry, fairly firm, and completely bloodless, structureless mass. The ultimate cause of the occurrence of this form of necrobiosis is probably to be sought in the infectious agent itself, in the toxic substances excreted by it. These toxins appear to be endowed with a certain reremote action, since caseation is sometimes observed in areas containing no tubercle fungi or only very few, while at some distance from the cheesy focus large accumulations of the fungi may be present. The process is not, as was formerly thought (Virchow), a mere desiccation or inspissation; for the caseating foci, as, for example, in cheesy pneumonia, sometimes exhibit a considerable increase in size in the course of their development. The process differs from simple coagulation-necrosis by the occurrence of a fatty change with the production of exceedingly fine granules, in addition to those phenomena which attend simple necrosis, such as karyorrhexis and karyolysis, with breaking-up of the nuclei into infinitely small particles and solution of the chromatin substances. This form of cellular death is also accompanied by the appearance between the necrobiotic cells of a firmly coagulated substance, which is evidently derived from the blood and which, on account of its morphologic and genetic similarity to fibrin, has been designated *fibrinoid substance* (Schmaus and Albrecht). It is probably the chief cause of the firmness and dryness of the cheesy, necrotic mass. In circumscribed tubercles the process of caseation always begins at the center and progresses in concentric lines toward the periphery; in the stained preparation the cheesy portions are characterized by their absolute loss of tingibility (Plate 38, Figs. 1 and 2). In the zone of advancing caseation karyorrhexis, with which we are already familiar, attended by the usual rearrangements of the chromatin, makes its appearance; the chromatin, after it has been broken up into minute splinters, ultimately

PLATE 40.

Fibrous Tubercle in the Apex of the Lung (Slaty Induration) (× 20.): 1, Cicatricial thickening of pleura with isolated foci of infiltration; 2, dense masses of coal-pigment deposited in the scar-tissue; 3, vascular spaces; 4, alveolar spaces with proliferated epithelium; 5, cheesy centers of the tubercles; 6, concentrically striated connective tissue surrounding the tubercles.

disappears. In diffuse tuberculous granulation-tissue caseation usually spreads uniformly, and is attended by the formation of large, cheesy necrotic superficial patches, as, for example, in the mucosa of the uterus, the ureters, and the pelvis of the kidney. Finally, the purely exudative tuberculous processes also undergo cheesy necrosis. When the exudate is purulent, it undergoes inspissation and a fatty change, with the production of minute granules and the formation of fibrin; when, on the other hand, the character of the exudate is cellulofibrinous, the cells are first converted into a cheesy mass of detritus, while the fibrin continues for some time to offer a successful resistance to the advancing necrobiosis. In this way, in cheesy hepatization of the lungs, for example, pictures are produced in which the central portions of the alveolar contents are completely converted into a cheesy mass; while the peripheral, exclusively fibrinous portion of the exudate and the interalveolar bridges, which are also fibrinous, are still practically intact (Plate 38, Fig. 1). Later the fibrin is also drawn into the area of caseation more and more; it loses its typical tinctorial reaction, although it may continue for some time to be demonstrable optically. In the end the process of cheesy necrosis involves the last remaining networks and trabeculæ of fibrin, and even the cellular structures of the alveolar walls, which up to that time have escaped. The elastic fibers offer the most obstinate resistance to the process of caseation, which they withstand for some time after all other structures have succumbed, and it is not uncommon to see in portions of the lung that have undergone complete cheesy degeneration, in which not a single nucleus retains its tingibility

Tab. 40.



and not a single cell-body or fibrin fiber is visible, a well-preserved elastic framework. (Compare *Atlas of Special Pathologic Histology*, Vol. I., Plate 42, Fig. 2, and Plate 43, Fig. 2.)

Foci that have undergone complete caseation frequently become the seat of secondary deposition of calcareous salts. At first these are deposited in the form of small, angular granules, which later coalesce to form larger nodules and masses resembling concretions; in the end the cheesy tissue may undergo complete mineral metamorphosis.

Another quite frequent termination of the tuberculous process is a *fibrous* or *fibroid change*. We have already learned that the so-called epithelioid cells in tubercle are genetically fibroblasts, such as are seen in ordinary granulation-tissue and represent derivatives of fixed connective-tissue and endothelial cells. As a rule, these fibroblasts do not realize the object of their development—*i.e.*, the production of fibrous connective tissue, because the toxic action of the tubercle fungi leads to cheesy necrosis of the entire cellular material before they have had time to do so. If, however, the tubercle fungi in the granulomata perish or their virulence is diminished, the tubercle may subsequently renounce the specificity of its inflammatory form (von Rindfleisch), in which case the epithelioid cells produce an abundance of fibrous connective tissue. If the center has already undergone partial caseation, the epithelioid cells usually arrange themselves in radiating lines around the cheesy center, and, after the protoplasm has disintegrated, may be gradually converted into connective-tissue cells. The fibrous intercellular substance forms communications with that of the adjoining tissue, with which it often combines to form a loose, reticular tissue, in the meshes of which the round-cells are seen in the same manner as in the case of lymph-follicles and their reticulum; or the formation of connective tissue may, from the beginning, take place in concentrically striated, circular masses, resulting in the deposition of successive layers of connective tissue around the cheesy or calcified center of the tubercle. After the cellular elements have disappeared this connective tissue may assume a hard, sclerotic character and completely isolate the necrotic focus. As a rule, this process is accompanied by a secondary formation of new connective tissue in the neighborhood, which joins the fibrous capsule of the tubercle and ultimately leads to the production of massive layers of connective tissue with diffuse induration, extending over large areas. The giant-cells, according to von Rindfleisch, also take part in the formation of the fibrous tissue by breaking up into spindle-cells, one for each nucleus, arranged in closely packed, parallel rows. [Hektoen has made similar observations in regard to giant-cells in healing tuberculous meningitis.—Ed.]

These indurative processes are observed chiefly in the lungs, especially in the apices. As the formation of new connective tissue causes the occlusion of numerous lymph-vessels, thus obstructing the channels by which inhaled foreign bodies are carried off, the inhaled coal-pigment usually forms large accumulations in these indurative foci and produces a slaty or blackish discoloration; hence the process is often designated *slaty induration* (Plate 40). Later the connective-tissue foci may undergo progressive shrinking and cause marked cicatricial retraction of the affected portions of the lung. The alveolar spaces that still survive in these affected areas usually do not communicate with the afferent bronchi, because the latter are obliterated by the cicatricial process. Accordingly, a proliferation of the originally smooth alveolar epithelium takes place in the remaining cavities in the lungs; the cells become taller and assume a cuboidal or cylindric shape, and the alveoli are converted into gland-like canals or tubes ("a typical epithelial proliferation"—Friedlander) (Plate 40).

2. Syphilis.

From the histological viewpoint syphilis also belongs to the tubercular diseases, and, like tuberculosis, not only causes the formation of tubercles [or nodules.—Ed.], but also leads to the production of diffusely distributed granulation-tissue in the body. The so-called *primary lesion* or *initial sclerosis* usually manifests itself as a simple inflammatory focus in the skin or in the affected mucous membrane. The papillary body is extensively infiltrated with round-cells and leukocytes, the blood-vessels are intensely injected, and the rete Malpighii also contains dense masses of leukocytes which may form actual perforations in the layer and cause the complete disappearance of the epithelium after separation of the stratum corneum, ultimately producing an ulcer (Hunterian chancre). Early in the process the blood-vessels of the cutis or submucosa become the seat of a marked accumulation of densely packed leukocytes. Similarly the so-called *syphilids* which appear on the skin and mucous membranes in the secondary stage present nothing that is microscopically typical. As a rule, they present circumscribed proliferative processes in the papillary body, with bulging of the epithelium, which at the same time often undergoes multiplication, and both corium and epithelium are thickly infiltrated with masses of round-cells (*condyloma latum; mucous patches*).

It is only in the tertiary stage that syphilis manifests the characteristics of a tubercular disease. Circumscribed granulomata develop much in the same way as in tuberculosis, often appearing simultaneously in a number of organs, as, for instance, the periosteum, the abdominal viscera, the adventitia of many blood-vessels, the soft membranes of the brain and cord, etc. At first these tumors present the greatest similarity to the granulomata produced by tubercle fungi, being composed in part of epithelioid and round-cells. Before long, however, certain differences become manifest, which make it possible, as a rule, to differentiate even the younger syphilitic formations from the genuine products of tuberculosis. The chief point of distinction is the behavior of the *blood-vessels*. In genuine tubercles—*i.e.*, structures caused by the tubercle fungus—all the preëxisting blood-vessels in the area of the tubercle early suffer occlusion, either by compression

PLATE 41.

Gumma from a Liver of a New-born Infant (× 280.): 1, Liver-cells; 2, fat-vacuoles in the liver-cells; 3, epithelioid cells; 4, giant-cells; 5, cross-sections of capillaries in the granuloma; 6, leukocytes and nuclear detritus.

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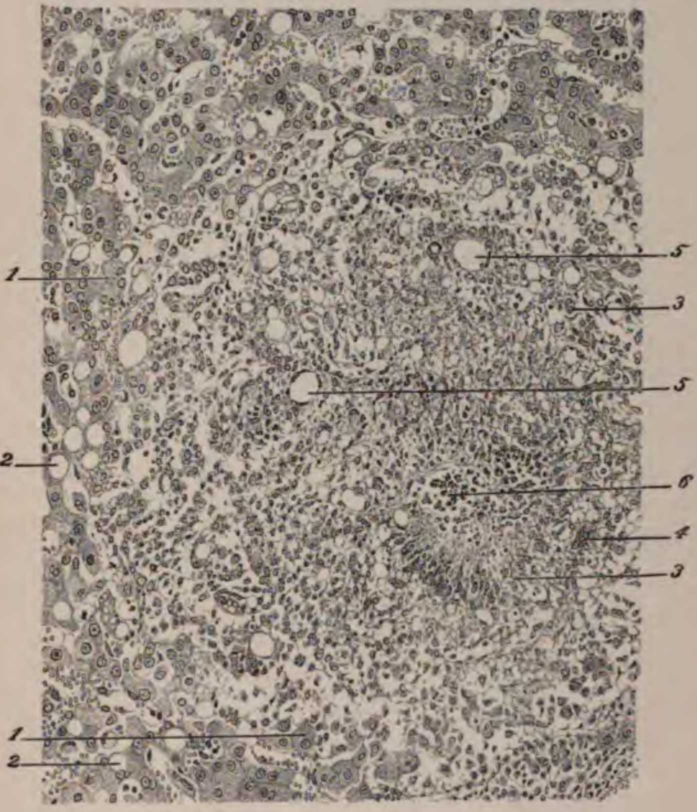
and thrombosis or by the encroachment of the proliferative process on the endothelium and the production of epithelioid cells. A new formation of blood-vessels never occurs in tubercles. On the other hand, the syphilitic granuloma, or *gumma*, as it is called, not only does not involve the blood-vessels of the affected tissue [gumma may develop in the adventitia.—Ed.], but is, on the contrary, characterized by the formation of new blood-vessels and capillaries which appear at the same time as the other cell. This capillarization of the new growth is practically always observed even in sharply circumscribed, nodular syphilomata (Plate 41). The epithelioid cells in gummata are, as a rule, regularly smaller, contain less protoplasm, and are spindle shaped and narrower than the analogous structures in tubercles. They are also, as a rule, less numerous than the round-cells, which are abundant from the beginning. Among the latter the polymorphonuclear leukocytes predominate largely; occasionally large groups of these cells may be seen at the very center of the focus (Plate 41).

Giant-cells are usually much more sparingly present than in tubercles. It would not be correct, however, to regard the presence of giant-cells with homogeneous (necrotic) centers and a polar arrangement of the nuclei as characteristic of tuberculosis in every instance, nor to base a differential diagnosis on their presence in the tissue; under certain conditions these cells may be observed in precisely the same form in syphilitic granulomata, just as, on the other hand, they are often altogether absent in genuine, especially rapidly growing, tubercles. It follows, therefore, that the giant-cell (type of Langhans) is never exclusively characteristic of tuberculosis; *but the* presence of giant-cells in great abundance should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always arouse a suspicion of a tuberculous infection, which always should be confirmed by the finding of tubercle fungi [or by the inoculation of guinea-pigs.—Ed.]. It seems as if occasionally combinations of syphilis and tuberculosis occur in the same granuloma (Baumgarten).

The luetic granuloma very soon evinces a marked tendency to fibrous metamorphosis, which is much more frequent and more extensive than is ever seen in tubercles. Sometimes the entire nodule is converted into a hard, fibrous mass; or there appears at the center a cheesy-necrotic focus, the periphery of which surrounds itself with a fibrous connective-tissue sheath derived from the epithelioid cells, and is at last inclosed in a dense capsule, the connective-tissue of which frequently undergoes hyaline change. This capsule is responsible for the hard, elastic consistence of the entire granulation tumor, and it has given it the name of *gummy* (india-rubber) *tumor*. Even after all these changes have taken place it is almost always possible to demonstrate blood-vessels in the fibrous capsules. [A rather characteristic feature of gummata is the irregularly wavy line of junction between the fibrous capsules and the caseous contents.—Ed.]

Finally the manner in which the cheesy necrosis makes its appearance presents certain typical differences, quite easily recognized after a little practice, thus enabling the observer to distinguish between syphilitic and tuberculous granulomata. The process of caseation progresses much more slowly in the gumma; the accumulation of nuclear débris is never so abundant as in the tubercle, because the disintegrating nuclei are always completely dissolved by karyolysis. The final product never exhibits the compact and inspissated character of a tuberculous cheesy mass; even when all the nuclei are completely destroyed, the rough outlines of the structure of the original tissue are always in the main recognizable. The blood-vessels persist a long time and may contain circulating blood-corpuscles, even in completely necrotic portions of the tissue. It is needless to say that cheesy gummata also may become the seat of calcareous deposits and that the necrotic substance may undergo complete calcification.

In new-born infants the subjects of hereditary lues, circumscribed syphilitic granulomata may be demonstrated in the liver, sometimes in the spleen, in the lungs, in the pancreas, in the suprarenal bodies, and in the kidneys; these granulomata do not differ in their cellular make-up from the above-described nodules. More frequently, however, hereditary lues manifests itself by the presence of *diffusely distributed granulation-tissue*, which also preferably attacks the liver and sometimes leads to considerable enlargement and induration of the organ (*Atlas of Special Pathologic Histology*, Vol. II., Plate 72, Fig. 2, and Plate 73). The parenchyma appears forced apart by a cellular tissue consisting chiefly of large spindle-cells and is traversed by thin-walled blood-vessels; in addition to the production of diffuse granulation-tissue circumscribed granulomata sometimes develop. The blood-vessels are, as a rule, extensively involved in the production of syphilitic granulation-tissue. The larger arterial trunks may be the seat of eruptions of adventitial gummata, which in their subsequent growth encroach on the other two arterial coats and, by compression, narrow the lumen more and more (*Atlas of Special Pathologic Histology*, Vol. I., Plate 10 b, Fig. 2). As a rule, however, the change is limited to the diffuse production of new connective tissue in the intima and media, which does not possess the same tendency to fatty degeneration as the connective tissue produced in atheromatosis and simple arteriosclerosis, and therefore results in the formation of an extensive fibrous growth in which hyaline degeneration of the bundles is often observed (see *Atlas of Special Pathologic Histology*, Vol. I., Arteritis). In the smaller arteries the process may produce complete occlusion of the lumen, often with conspicuous proliferation of the elastic fibers between the newly formed threads of connective tissue.

3. Leprosy.

Lepra, or leprosy, a disease caused by a short bacillus discovered in 1880 by Armauer Hansen, also manifests itself, as a rule, by the production of granulomata. These nodular formations are never so distinctly circumscribed, however, as in tuberculosis and syphilis. They do not take the form of a "tubercular disease," the lesions being, as a rule, quite diffuse, appearing on certain mucous membranes and on the external skin. The nasal mucous membrane is involved more prominently than any other mucous surface, and is, in fact, regarded as the usual port of entry of the lepra fungus (Sticker). The bacilli are usually imbedded in the form of bundles like bunches of cigars in large multinuclear cells with an abundance of protoplasm, which are probably derived from proliferated fibroblasts. The cutaneous enlargements are produced chiefly by masses of large, spindle-shaped and stellate fibroblasts, which are later joined by numerous small round-cells, but rarely by leukocytes. The giant-cells seen in the lesions of leprosy usually consist of large clumps of protoplasm with numerous vacuoles. The epidermis overlying these areas of cellular proliferation may exhibit increased thickness of individual layers, especially of the stratum corneum, while in the rete Malpighii disappearance of the nuclei and the formation of vacuoles are observed. The bacteria often collect into enormous masses or in the form of spheric clumps of zoöglea. The formations usually cause increased thickness of the skin, which is thrown into folds and more pronounced irregularities, assuming a pasty appearance from the formation of numerous vacuoles filled with fluid.

In most cases the nerves are invaded prominently by bacteria; the bacteria for the most part are intracellular and penetrate the perineurium as far as the sheath of Schwann, gradually causing disintegration of the axis-cylinder and, of course, interrupting the conduction of the affected nerves (*anesthetic leprosy*). Sometimes regenerative phenomena are observed in the nerves, with

PLATE 42.

FIG. 1.—**Actinomycosis of the Pleura** (Alum-cochineal; Gram. × 42.): 1, Central network of threads; 2, rays of the actinomycelial kernels covered with club-shaped terminations; 3, accumulations of leukocytes around the threads; 4, newly formed, concentrically striated connective tissue.

Fig. 2.—**Teased Preparation from Actinomycotic Granulation-tissue, with Numerous Finger-shaped Clubs** (× 745.).

FIG. 3.—**Bothryomyces Granules from Bothryomycotic Granulation-tissue from the Lung of a Horse** (× 200.).

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multiplication of the nuclei in the sheaths of Schwann (Babes).

4. Actinomycosis.

The disease caused by the ray fungus [more properly ray fungi.—ED.] is also, as a rule, characterized anatomically by the development of diffusely distributed granulation-tissue. The fungous clumps, consisting of a central mass of threads and peripheral rays with club-shaped terminations (Plate 42, Figs. 1 and 2), are imbedded in dense accumulations of leukocytes, which often exhibit an advanced degree of fatty degeneration. These masses of leukocytes are so distinctly circumscribed and so abundant that they give the impression of genuine abscess-cavities. They are bounded externally by embryonal connective tissue, evidently of recent production, which is composed of the now familiar constituents, fibroblasts and a variable number of round cells (Plate 42, Fig. 2). Newly formed blood-vessels may also be present in considerable numbers. As a rule, if fibers have already been formed, this connective tissue exhibits a distinct, concentric striation, the many layers of which adapt themselves to the surface of the small pus-cavities. In young fungous clumps, surrounded by only a moderate accumulation of leukocytes, giant-cells are occasionally recognized. Sometimes an opportunity of studying the entrance of the fungi into the tissues of the body more accurately is afforded; foreign *bodies*, usually of a vegetable nature, such as beards of

Tab.42.

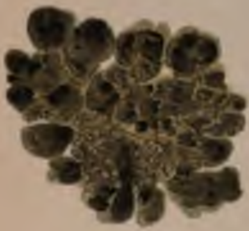


Fig.3.

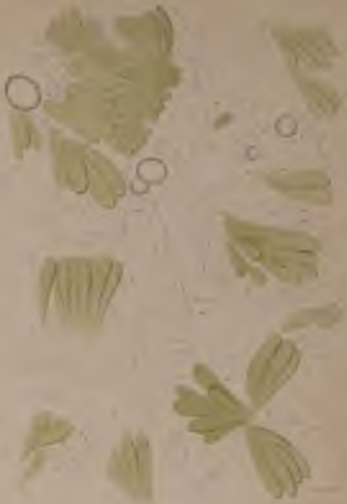
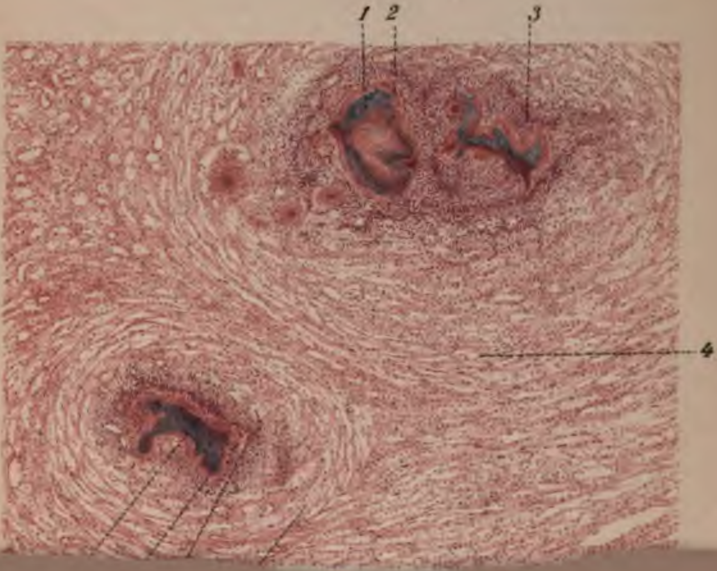


Fig.2.



different kinds of cereals, fragments of grass, and the like, may be found in the granulation-tissue, and from these foreign bodies the ray fungi are seen growing into the surrounding tissue. Within these vegetable foreign substances the proliferating fungi are seen to consist exclusively of threads; but wherever they project beyond the walls of the vegetable structure and come in contact with the adjacent tissues of the body the threads at once throw out the club-shaped enlargements, like caps surmounting their extremities, showing that the penomenon represents a kind of protective action on the part of the micro-organism against the injurious influences of the juices and cells of the body. [In certain forms of actinomycosis club-shaped enlargements of the ends of the threads may not form.—Ed.] As the new formation of concentrically striated connective tissue progresses actinomycotic granulomata may be converted into a hard, cicatricial tissue; the fungous clumps may perish in the organism, and then usually undergo a kind of calcification, although their shape is not at first affected.

[Occupying a place intermediate between typical actinomycosis and tuberculosis are a number of actinomycelial diseases—*i. e.*, infections caused by branching, filamentous fungi, some of which are distinctly acid-proof.—Ed.]

There is another form of granuloma which is in many respects similar to actinomycosis and occurs chiefly in horses, beginning usually in the stump of the spermatic cord in geldings; it is characterized by the formation of a hard, brawny tissue containing numerous abscess cavities. Within the cavities characteristic clumps are found of a fungus which is called *bothryomyces* (Bollinger). The entire process received from its discoverers (Rivolta and Johne) the name *mycodesmoid* or *mycofibroma*. It occasionally gives rise to metastasis, and may then lead to the formation of multiple deposits resembling fibromata, especially in the lungs, containing large and small collections of leukocytes with fungous clumps imbedded among them (Bollinger). The latter take the form of irregularly lobulated, fissured structures resembling cauliflower (Plate 42, Fig. 3). With suitable stains, Gram's for instance, it is possible to demonstrate within these structures innumerable spheric elements of uniform size, surrounded by a vitreous membrane. They have accordingly been interpreted by many authors as zoögloea of *Staphylococcus pyogenes aureus* (Kitt). [It is, therefore, probable that this disease is not etiologically related to actinomycosis. A similar disease of as yet unknown etiology occurs in swine, especially in the stump of the spermatic cord after castration. Here, mention should be made of **blastomycosis** (Gilchrist), or **oidiomycosis** (Ricketts), a chronic infection, especially of the skin, caused by fungi which, in the lesions, appear as double-contoured and budding yeast-like bodies, but which in cultures may form hyphæ. Histologically the lesions bear some resemblance to tubercles, but there is no caseation, and there are miliary accumulations of polymorphonuclear leukocytes. (See Rickett's *Oidimycosis, Blastomycosis of the Skin and its Fungi;* and Dürck's *Special Pathology and Histology*, section on the Skin).—Ed.]

V. TUMORS.

The term tumor, neoplasm, or blastome is applied to more or less circumscribed,[1] superfluous new formations of tissue, growing independently and without any physiologic limitation, which at no time of their existence form integral parts of the organism, and as they grow are from the outset quite independent of functionating organs. It is evident from this definition that the domain of tumors touches at certain points that of other progressive tissue-reactions. This is the case as regards regeneration of destroyed tissue; but we have already seen (see Regeneration) that the proliferation which follows wounds and destruction of organs goes on to a definite physiologic limit, the defect being either more or less completely made good by specific parenchymatous tissue capable of function, or the original tissues replaced by an indifferent reparative tissue, which takes the place of the original cells. In the second place, the line must be drawn between true tumors and certain inflammatory tissue proliferations which may often be associated with considerable increase in volume, and especially with the formation of circumscribed foci of proliferation. This takes place chiefly in the so-called infectious granulomata, which formerly were included among the neoplasms.

In order to make the distinction clear, it is now customary to include among genuine neoplasms only those new formations of tissue in which a specific tissue-reaction to the invasion of an infectious agent (such as the poison of tuberculosis, syphilis, glanders, lepra, etc.), can be excluded, at least in the light of our present knowledge.

Some investigators have regarded microparasites, either bacteria or protozoa, and, in quite recent times, especially blastomycetes, as the etiologic agents in the production of tumors; but the theory has not so far been proved for a single genuine tumor. Nor has the attempt to produce a tumor artificially by the experimental introduction of such forms of life so far proved successful.

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[1] Not all tumors present the picture of a circumscribed new formation of tissue. There are also genuine neoplasms in the serous membranes, for example, which appear as diffuse growths, extending over a large surface, and do not at any point produce a true "tumor-node."

The essential difference between infectious growths and genuine tumors is that when the former are reproduced by metastasis, the *parasite* itself is conveyed in the blood and incites at the metastatic site new formation of tissue similar to that of the parent growth; whereas in the case of genuine tumors, metastasis takes place by the transplantation of a part of the parent tumor, which then begins to proliferate independently at the new site.

Broadly speaking, tumors are composed of the same elements as the normal tissues of organs; but there is a general tendency to the persistence of embryonic cells and immature forms of tissue, especially in the tumors which originate from the connective-tissue group. As a rule, several different kinds of cells are necessary for the production of a tumor; only in exceptional cases is a tumor built up of only one kind of cells, and even in those cases the formation of a vascular system to supply the newly formed cell-complexes is required and is effected by the simultaneous growth of blood-vessels.

Tumors are classified according to the various tissue-elements and kinds of tissue that take part in their formation:

1. Tumors of the *connective-tissue group.* These neoplasms grow from mesodermal tissue germs, in so far as the latter form the supporting framework of organs. As they consist of only one kind of tissue and never imitate the structure of a complete organ, they are often designated *histoid* tumors.

2. Tumors formed chiefly by the *proliferation of epithelial cells.* As these cells are incapable of forming large aggregations unless they are traversed and nourished by blood-vessels, because they would otherwise very soon die for want of nutritive material, these epithelial masses regularly contain a more or less abundantly developed

vascular supporting tissue (stroma). Owing to this arrangement the structure of these tumors much more vividly suggests the histologic picture of functionating organs than does that of the simple connective-tissue tumors; for it is possible to distinguish a tumor parenchyma, as it were, represented by the aggregations of epithelial cells, and a stroma. This group of tumors is, therefore, also called the group of *organoid* tumors.

The entire absence of any physiologic function is not an absolutely indispensable characteristic for the definition of a neoplasm, and in many organoid tumors secretory processes may be observed, such as are otherwise present only in true organs; thus, for example, the formation of goblet-cells and the production of mucus by these cells in adenomata, the production of bile-pigment in glandular tumors of the liver, and so on.

3. *Mixed tumors.* The parenchyma of these tumors may consist of a great variety of tissues, which may be in part highly differentiated and may belong either to the connective-tissue group or to epithelial structures. These tumors are, therefore, extremely complex in their structure, and are known also as "*teratoid*" tumors.

A subdivision of this group embraces tumors which not only are composed of different kinds of tissue, but harbor within their substance true organs or rudiments of organs. These tumors are called *teratomata* (miraculous tumors), or, since they owe their origin exclusively to the displacement and inclusion of aberrant germs in embryonal life, they are also designated "*embryomata.*"

Their identity with tumors occurring in postfetal life is, therefore, altogether external.

While this classification is useful from a practical standpoint, it cannot be denied that it lacks biologic foundation and cannot be carried out rigorously; for the word "epithelium" does not refer to a special cell-form, but is intended solely to describe a certain aggregation of cells for covering a surface or lining a cavity. In itself an epithelial cell may present exactly the same appearance as a connective-tissue cell.

It is in many cases difficult, and in most cases of so-called "malignant" tumors quite impossible, to determine accurately in what normal tissue-cells the neoplasm has had its inception. If the outline of the individual cell is taken as a guide, the neoplasm may equally well be regarded as an epithelial or as a connective-tissue growth; it is possible, however, to determine whether the cells are arranged in a continuous "epithelial" aggregation or whether the cellular elements are separated from one another by an intercellular substance. In the former case, the presence of a stroma arranged in the form of a meshwork results, generally speaking, in the production of tumors of alveolar structure; in the latter case the structure of the neoplasm is more diffuse, although it would be impossible in every individual case to tell whether the growth started in true epithelial or in connective-tissue cells.

The shape of the cell alone must never be taken as a criterion by which to judge the genesis of a tumor. Hence there is no such thing as a "carcinoma cell" or a "sarcoma cell"; the type of a tumor, whether it be epithelial, connective-tissue, or mixed, can be determined positively only by the arrangement of the cells with regard to one another. For this reason extreme caution is necessary in giving an opinion on the character of a tumor from an examination of isolated tumor-cells.

Even the term "epithelioid" cell, suggested by Virchow for the cells in tubercles, was not intended to designate a special form of cell, but merely the external covering of these granulomata by large, plasmatic cells resembling epithelium.

All the cells of the organism possess the faculty of becoming the starting-point of tumors. The exciting cause for the production of the sudden, independent growth of a special cell-complex—*i. e.*, the ultimate cause of tumor-formation—is a question about which we are still totally in the dark. It seems reasonable to assume, however, that those cells which form the beginning of a tumor lose certain specific faculties to form organs; in a sense they are reduced to a lower level and suffer a change the reverse of differentiation [*entdifferencierung.*—Ed.] and lose the power of transmitting to their descendants the property of acting as functional units in the organism. Instead, they place themselves in a more or less far-reaching emancipation from the parent organism, and from that time on become a useless, superfluous, or even directly hostile and destructive formation. This functional separation from the matrix, which frequently finds its morphologic expression in modifications of cell-proliferation and cell-formation, has been called by Hansemann *cellular anaplasia.*

The extent to which the cells of tumors deviate morphologically from the cells of the matrix is extremely variable. In the simplest cases the tumor-cells preserve their original shape and arrangement.

Thus fibroma, for example, is usually composed of typical connective-tissue fibers and cells; a carcinoma of the stomach represents a reproduction of the normal cylindric cells; epithelial tubes containing goblet-cells are frequently found in cancer of the intestine; and in certain forms of skin cancer all the epithelial layers of the epidermis are fully developed.

On the other hand, the character of the cells in the neoplasm may present great modifications, and in such cases the shape and arrangement of the tumor elements afford no information whatever in regard to the nature of the matrix; for some cylindric cells may suffer metamorphosis into cuboidal or polygonal cells, and may even appear in the tumor as squamous epithelial cells, as in many cancers of the uterus.

It follows, from what has been said, that the modification in the tissue of a tumor and its deviation from the histologic character of its matrix are very much more pronounced in some cases than in others. A general distinction is made between neoplasms which reproduce or, at least, imitate the structure of the matrix,—*homologous tumors*—and those which fail to exhibit any analogy with the matrix—*heterologous tumors.* Histoid as well as ganoid neoplasms may be homologous or heterologous tumors; for it is obvious that a chondroma starting in the cartilage of a joint repeats the structure of the organ which forms its starting-point, in the same way as an adenoma of the mammary gland, for example; while in the case of a round-cell sarcoma of the periosteum, for example, or of a carcinoma of some gland, this structural analogy is not observed. It is not always an easy matter to determine, in a given case, from the histologic structure alone, whether a tumor is homologous or heterologous; a simple papilloma, for example, may sometimes exhibit a typical epithelial proliferation and differ widely from the picture of its parent tissue, and yet it would have to be regarded as a homologous tumor; and, conversely, it may be difficult in the case of a cancer of the external skin to recognize the heterologous nature of the structure.

In general, a heterologous tumor is one in which the cells have undergone a metaplasia, but the two terms are not quite synonymous; for even in a carcinoma—for instance, a goblet-cell carcinoma of the intestine—cellular metaplasia may be very faint, as we have already shown.

On the other hand, it is altogether *wrong* to use the terms "benign" and "malignant" as equivalent to "homologous" and "heterologous." These terms should be avoided altogether in reports of histologic examinations; for a tumor is regarded as malignant whenever it can be shown that—(1) It encroaches upon and destroys neighboring tissues (the destructive effect on the neighborhood of mere pressure is, of course, a different matter); or (2) that it gives rise to metastasis and local return after removal—recidivation. Now, it is to be remembered that practically every known tumor may, under occasional circumstances, give rise to metastasis and thus register itself as a malignant growth; for this has occurred, in rare instances, even in the cases of fibroma, myoma, chondroma, and adenoma. We only know empirically that the so-called homologous tumors *usually* do not give rise to metastasis; but there is not one single *anatomic* feature by which it would be possible to determine from the histologic examination of a tumor whether it is benign or malignant. [Generally speaking, the presence of numerous mitotic figures in the cells of a heterologous tumor is regarded as an indication of malignancy.—ED.]

All that can be said in a given case is that, so far as appears from the microscopic examination, we have to deal, for example, with an adenoma, and that we know that in the great majority of instances such a tumor is benign; but even the most experienced examiner will not venture to guarantee that the tumor will prove benign. Conversely, tumors characterized by a heterologous structure and extensive metaplasia of their cells sometimes continue to behave clinically like benign tumors, at least for a long time. It is needless to say that the benignancy or malignancy of a tumor depends to a great extent upon its seat; thus, for example, a tumor which in itself is benign —*i. e.*, is not destructive in its growth and does not give rise to metastasis—may, if it be situated in the brain, have the significance of a malignant tumor as regards health and life (*quoad valetudinem et quoad vitam*).

The growth of tumors follows the same laws of cell-proliferation as the growth of normal tissue or tissue in the process of regeneration. Accordingly, karyokinetic figures are often observed in the tumor-cells, and it may be said that the frequency of this phenomenon is a good criterion of the rapidity of the tumor's growth.

The position of the proliferation-axis of the cells engaged in mitotic division is not, however, a trustworthy indication of the malignancy of a tumor; for the axis of proliferation of the dividing cells—*i. e.*, the line which connects the two centrosomes—may occupy any direction in space, even in normal cell-division.

In rapidly growing and especially in heterologous tumors, there frequently occurs, in addition to the regular mitosis, anomalous, indirect division of both the nucleus and the cell-body, presenting another difference between tumor-cells and normal cells of organs. The irregularities affect both the achromatic substance and the chromatin of the nucleus. As regards the former, instead of the regular, bipolar mitosis, it is not uncommon to find mitosis presenting three or more, and sometimes innumerable, attraction-spheres or centrosomes, in which the rearrangement of chromatin gives rise not to two, but to a correspondingly large number of nuclei. These abnormal karyokinetic figures are called multipolar.

Quite frequently cell-division fails to keep pace with the division of the nucleus, and polynuclear cells, *polykaryocytes*, or *giant-cells* are produced.

Irregularities are even more frequently observed in the nuclear chromatin in tumors; for the "fragments," nuclear rods, or chromatosomes which result from the mother-skein, or spirem, often exceed the normal either in number or in size (sometimes very greatly), or, on the other hand, may be below the normal. In the former case we speak of *hyperchromatosis;* in the latter, of *hypochromatosis* of the nuclei. Hyperchromatic division-figures frequently present the picture of irregular, exceedingly large rosets, and are called *giant mitoses;* they sometimes consist of hundreds of individual chromatosomes, distributed either between two or among three centrosomes. Very rarely, and practically only in carcinoma, *asymmetric mitoses* are observed, in which the two resulting daughter-stars receive a different quantity of chromosomes. It is, therefore, important, in judging a specimen, to remember that the nuclei in process of division, if they are cut obliquely, sometimes simulate asymmetric mitoses. The hypochromatic nuclei are distinguished by their small number of chromosomes; or the chromosomes themselves may be unusually small, with short and very thin loops. Sometimes particles of chromatin that have not been used in the division and have become displaced are found near the mitotic nucleus, a phenomenon which occurs in other pathologic processes and occasionally even in normal cell-division.

A knowledge of the relation of tumors to the adjacent tissue is of the greatest importance for the understanding of their biologic position. The chief characteristic of genuine tumors is their high degree of independence. Their enlargement is not the result of a simultaneous or successive homologous proliferation of contiguous portions of tissue—*i. e.*, the same hyperplastic process does not extend over a large area; on the contrary, in almost every case it may be assumed, if it cannot be actually demonstrated, that the tumor has originated from the multiplication of a certain cell-complex which may be regarded in a sense as the germ of the tumor. This is the essential difference between a tumor and simple *hyperplasia*, or inflammatory processes followed by an increase of tissue.

Thus, for example, in the growth and spread of a skin cancer the epithelial layers near the point of its origin do not undergo the same atypical proliferation; there is not, in any sense, an infection of the surrounding tissue; the increase in the size of the tumor is due solely to the fact that the descendants of the original germinal cells of the tumor multiply *ad infinitum* and grow into the surrounding tissue. This is the case also in the so-called benign tumors, as, for example, fibroma, myoma, lipoma, etc. We may say, therefore, that the tumor grows "unicentrically"; it originates, in the first instance, from a single center.

There is no doubt that this mode of origin is far more frequent than any other in all forms of tumors, although I will not deny that a neoplasm may occasionally have its starting-point in several germs separated from one another by varying intervals. The process would then be called a "multicentric" tumor-formation, and it appears that these multiple, simultaneous starting-points occur chiefly in diffuse tumors of the external skin and of the serous membranes. But the occurrence of multicentric tumors does not militate against our fundamental conception of the genesis of tumors. The phenomenon does not, as was formerly supposed, consist of a degeneration attacking the individual cells of an organ in succession, and converting them, as well as their descendants, into tumor-cells; on the contrary, the germ of the tumor is hidden within the tissue; one cell-group in an organ is endowed with the

FIGURE VIII.

Atypical Mitotic Figures from a Large-cell Sarcoma of the Periosteum (× 745.): *a*, Giant mitosis; *b*, *c*, *d*, irregularly shaped mitoses with degenerated chromosomes; *e*, equatorial plate with dislocated chromosomes; *f*, triaster with displaced chromosomes.

FIGURE IX.

Cells from a Large-cell Sarcoma (× 745.): *a*, *d*, *e*, Nuclei in various stages of nuclear degeneration; *c*, multinuclear cells; *b*, fat vacuoles in the protoplasm of a cell, the nucleus consisting of a conglomeration of constricted chromosomes; *f*, multinuclear cell containing a leukocyte.

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power of unlimited, irregular growth. Some unknown force, the essential nature of which has so far completely escaped our knowledge and our comprehension, is capable of calling forth this latent power of proliferation, and the germ begins to grow *out of itself*, like a seed that has been buried in the ground. The surrounding tissues of the body remain passive.

But the composite organoid tumors, no less than the more simply constructed histoid neoplasm, require for their subsequent growth a connective-tissue stroma and a certain number, at least, of blood-vessels to nourish them, and these constituents are derived from the matrix, and, as the tumor continues to grow, from the tissue which it invades. Thus, a fibroma—*i. e.*, a circumscribed, independent new formation of connective tissue—would soon perish if it were not vascularized by the preëxisting blood-vessel at its point of origin. An epithelial new growth requires, in addition to blood-vessels, a certain quantity of connective-tissue stroma, which it simply derives from the invaded region. This condition is readily demonstrated in the case of metastases. Thus, a metastatic glandular cancer, which has been carried to a distant point from the parent tumor through the lymph- or blood-stream, consists solely of a group of epithelial cells, as may frequently be observed (Plate 77, Figs. 1 and 2), and would not be able to develop in an unlimited manner were it not for the nutritive material brought to the cells by the vascular

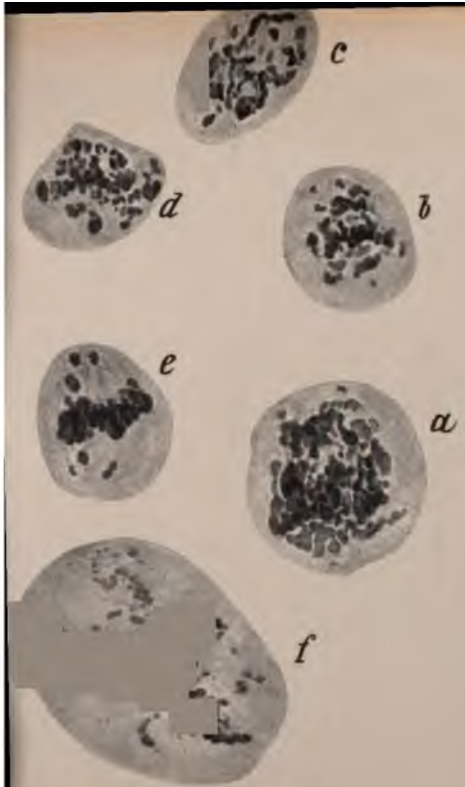


Fig. VIII.

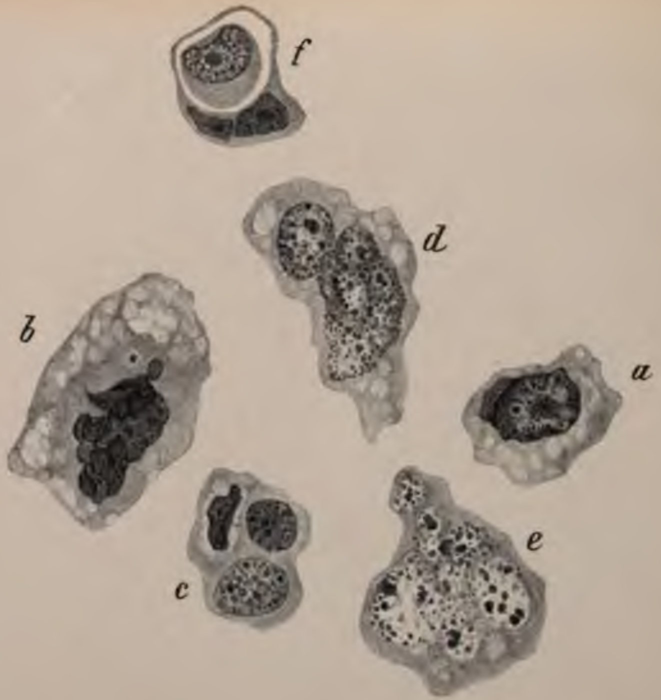


Fig. IX.

connective tissue of the invaded area. In this sense, therefore, all tumors are to a certain extent dependent upon the parent organisms.

As the tumor continues to grow the stroma itself often undergoes certain alterations; as a rule, it is much more rich in cells than in its original state, because the tumor calls forth a variety of inflammatory reactions in the surrounding tissue; hence the boundary of the neoplasm particularly is often more or less thickly infiltrated with leukocytes. In many cases, epecially in rapidly growing, heterologous tumors, the blood-vessels present a distinctly embryonal character, lacking the typical development of the several layers; the elastic and muscular tissue, especially, is imperfectly developed, and even large blood-vessels appear to be mere endothelial tubes.

The effect of the tumor on the neighboring tissue, as its volume continues to increase, depends on whether or not the tumor maintains its original nodular form.

In the former case it remains distinctly separated from its surroundings; yet, if the tumor grows rapidly, the adjacent tissue may be greatly damaged by pressure or by certain chemic influences emanating from the tumor. Thus it is well known, for example, that the pressure of a growing tumor will cause complete atrophy of contiguous bones. The neoplasm may be compared to a tuber growing in the earth and pushing aside the surrounding soil. This mode of enlargement is known as *expansive growth*, and may be due chiefly to cell-proliferation in the inner portions of the tumor, similar to the growth of lymph-follicles from a germinal center (*central growth*), or to increased proliferation at the periphery causing a continuous apposition of new elements (*peripheral, appositional growth*). On the other hand, the effect of the tumor on its surroundings may be quite different either from the very beginning or during the subsequent course of its growth; the primary nodule may throw out root-like processes and radiating extensions into the neighboring tissue. It is the similarity of such a tumor with the figure of a sea-crab that gave rise to the ancient

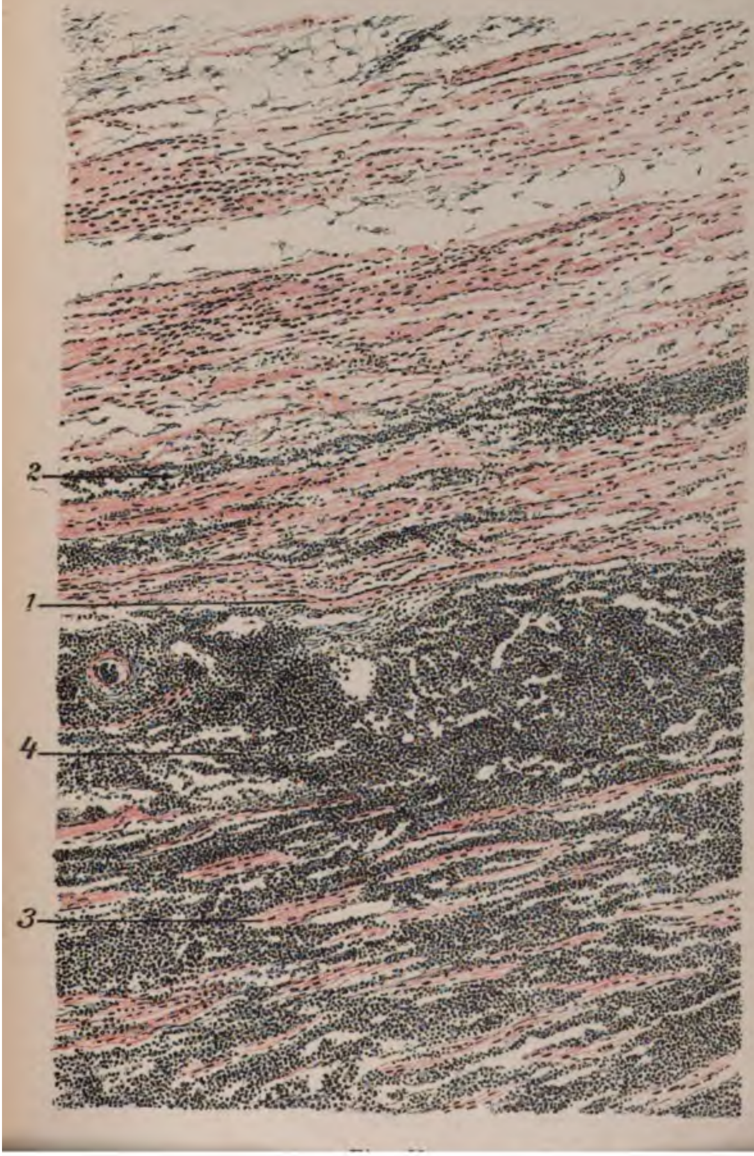
FIGURE X.

Infiltrating Growth of a Small-cell Sarcoma in Muscle (× 70.): 1, Muscle-fiber showing an increase of the nuclei in the sarcolemma; 2, narrow aggregations of sarcoma cells between the muscle-bundles, which have been forced apart; 3, remains of muscle-fibers in 4, dense masses of sarcoma-cells.

"cancer." This method of extension is known as infiltrating growth, and often makes it extremely difficult to separate the neoplasm from the surrounding tissue. In fact, in many cases this is quite impossible, at least macroscopically, and the picture of a diffuse hyperplasia may be the result, as, for example, in infiltrating gastric cancer, in certain forms of sarcoma, and even in some fibromata and lipomata.

As there is no physiologic limit to the growth of a neoplasm, *retrograde metamorphoses* are exceedingly frequent, and tumors are subject to the same degenerative changes as the normal structures of the body.

Fatty degeneration in particular is frequently observed in tumors. It may be said in general that the extent of fatty degeneration is directly proportional to the degree of anaplasia in the cells, and it is accordingly, as a rule, more pronounced in the so-called malignant tumors; although the neoplasms ordinarily called benign in exceptional cases may also present a quite extensive fatty change. There is a direct relationship between fatty degeneration and the vascularity of a tumor: the more defective the latter, the more rapid and more extensive will be the fatty degeneration. It is, therefore, as a rule, much more intense in organoid tumors, especially in carcinoma with large islands of tumor-parenchyma, than in the ordinary histoid neoplasms, which are more evenly supplied with blood-vessels. In the former the fatty degeneration is almost always limited to the tumor-parenchyma, the stroma, as a rule, escaping, at least for a long time, or exhibiting only an insignificant sprinkling of isolated foci of degeneration. Kinks, constrictions, or obstructions of blood-vessels by tumor-thrombi often become the cause of fatty degeneration.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As in normal cells, fatty degeneration sets in with the appearance of a few shining fat-globules in some of the cells. In tumors of alveolar structure the degeneration almost always begins in the central portions of the cell-masses that fill the alveoli. The droplets become more and more numerous and larger; often a large part of the tumor appears almost uniformly covered with exceedingly minute, almost dust-like granules of fat, which give the well-known reaction with osmic acid and with sudan red. Sometimes large fat-drops predominate in the cells, or drops of every conceivable size may be present at the same time. Tumors of considerable size have been observed in which it was barely possible to demonstrate a single cell in a reasonably normal state. Soft carcinomata with but little stroma and certain epithelial renal tumors —the so-called hypernephromata—exhibit a marked tendency to the accumulation of fat in their cells. When sections of these tumors are examined after treatment with alcohol, etc., the fat is of course extracted, and in the place of its droplets and larger globules there is found nothing but the vacuoles in the cytoplasm which originally had been occupied by fat; in cases of extensive fatty degeneration the structure of the cell-bodies completely resembles that of foam. If the degeneration progresses still further and the fat is deposited in ever-increasing quantities, the cells are gradually destroyed, and by their disintegration the fat-droplets are liberated and converted into a semifluid, yellowish-white mass which oozes from the alveoli in the form of a milky fluid (*cancer juice*) or in the form of more consistent, whitish plugs resembling comedones. On microscopic examination these are found to consist almost entirely of free fat mixed with a little nuclear débris. In rare cases the interstitial tissue of the tumor is also attacked by the fatty degeneration; the fat-droplets arrange themselves in spindle-shaped or chain-like masses corresponding to the shape of cells and of fibers; in few cases, indeed, does complete disintegration take place.

Almost all cases of fatty degeneration exhibit at the same time, or slightly preceding it, certain definite alterations in the nuclei. These changes also are more common and more extensive in markedly anaplastic tumors than in tumors the cells of which deviate comparatively little from the normal. These changes affect principally the chromatin framework, which is greatly increased in quantity and presents a most irregular arrangement, giving rise to greatly swollen and very large, so-called *giant nuclei.* The nucleoli are often increased in number or materially so in size; they may give special tinctorial reactions, different from the rest of the chromatin, so that at the first glance they appear to be something extraneous and not belonging to the nucleus; their marked affinity for acid anilin stains has often caused them to be mistaken for foreign organisms—*i.e.*, parasites, especially blastomycetes, or even as to the causes of cancer *par excellence.* But as the cellular degeneration progresses, more profound changes make their appearance in the structure of the nucleus; the chromatin disappears more and more from the nuclear vesicle, and deposits itself in the form of flakes, clods, or lenticular or otherwise irregular masses along the nuclear membrane, to which it thus imparts a circular or quite irregular thickening—*hyperchromatosis of the nuclear wall* (Klebs), *pyknosis* (Schmaus and Albrecht). This is then followed by interruption of the ring at one or more places and destruction and fragmentation of the chromatin *karyorrhexis.* Owing to the escape of individual particles of chromatin a variety of figures resembling biscuits or horseshoes or sometimes mulberries are produced, and ultimately break up into smaller and ever smaller pieces (chromosomes), and finally into minute particles or splinters still capable of taking the nuclear stain. Finally, even the latter are dissolved and extensive areas of the tumor may appear completely devoid of nuclei, a phenomenon that is exceedingly frequent in almost all large neoplasms.

It is needless to say that when mitotic figures are present they also are attacked by the degenerative process. The commonest result is the conversion of the chromosomes into shapeless, unrecognizable, branching structures, or the destruction of the spirem, mother-star, or disaster leads to the production of most irregular, rose-like figures, which must not be confounded with hyperchromatic mitoses. Complete solution of the karyokinetic figures may also take place at any stage of their development and register itself by partial loss of tingibility.

Whether or not fatty degeneration is present, the cells often contain pellucid, spheric, lenticular, or rarely polygonal bodies, which may yield a great variety of tinctorial reactions. When they take the nuclear stain they are often derived from leukocytes that have invaded the tumor-cells, have lost their cell-bodies through disintegration, and whose nucleus has undergone fragmentation or irregular contraction. These structures are particularly frequent in cancers consisting of squamous epithelial cells. It is, however, much more common for these bodies to be hyaline,—that is, totally devoid of structure,—or to exhibit only a suggestion of concentric formation. Sometimes they are greatly swollen with water and take up the greater part of the cell-body, crowding the nucleus to the wall in the form of a kidney-shaped, crescentic, or sickle-shaped body. Virchow was the first to describe these structures, which he called *physalids* (*φῦσα* = bladder). Recently they have again come into prominence because some authors believe they have found in them the much-sought-for cancer parasites. All these so-called *cell-inclusions* may be present with more or less pronounced degeneration of the nucleus. If cells and nuclei are completely destroyed by fatty degeneration and disintegration, the inclusions, of course, are liberated and appear in the microscopic preparation as deeply stained, usually spheric bodies, imbedded in the necrotic tissue; they also form some of the structures described as *Russel's corpuscles*, which are distinguished by their great affinity for fuchsin.

The nuclei in the tumor-cells very often present budding and fragmentation, resulting in the production of irregular, lobulated nuclei and sometimes basket-shaped structures. If complete constriction takes place repeatedly, the so-called parenchymatous giant-cells are produced, which are observed in many forms of tumor. These cell-formations are usually distinguished quite readily from true polykaryocytes, such as occur in so-called giant-cell sarcoma, and from the foreign body giant-cells and the giant-cells occurring in tubercles and in gummata by the irregular size of their nuclei, which really represent only nuclear buds and are often connected by threads (Fig. IX.).

In addition to fatty degeneration all kinds of tumors frequently represent a partial and sometimes extensive *caseation.* In most cases it is to be regarded as due to anemic infarction secondary to thrombosis or embolism of the supplying blood-vessel, or to tortion, kinking, constriction, or compression of the pedicle. The caseation may be accompanied by a low grade of fatty degeneration. But the necrosis is chiefly brought about by a process of albuminous coagulation, as explained in connection with the subject of necrosis. Fibrin is formed in the interstices between the necrobiotic cells, or, at any rate, a homogeneous, fibrinoid substance. In the nuclei the processes which lead to karyorrhexis and ultimately to karyolysis are observed, the same as were described in connection with fatty degeneration and as are also found in cheesy degeneration of tuberculous tissue.

Cheesy portions of tumors may become impregnated secondarily with calcium salts; but in many varieties of tumors *calcification* takes place without any distinct caseation. In all such cases it is possible to demonstrate some diminution in the supply of nutritive material, occlusion, or thickening of the vessels with narrowing of their lumen.

The calcium deposits itself in minute particles, at first as fine as dust, which gradually coalesce and form large homologous cords or concentrically striated spheres. They yield the usual tinctorial and chemic reactions (see Degeneration). Sometimes a large portion of a tumor, or even the entire growth, as, for example, in the case of uterine myoma, may be converted into a compact, calcified mass of stony hardness, without a trace of the organic substance. The lime is usually combined with carbonic acid, and sometimes also simultaneously or even chiefly with phosphoric acid, and gives the gypsum reaction on the addition of sulphuric acid. Certain tumors—the so-called *psammomata*—in which calcareous deposits are the rule owe their name to this distinguishing characteristic.

Epithelial neoplasms not infrequently exhibit a pathologic process of *cornification*. This occurs not only in carcinomata, originating in epithelial cells that are normally cornified, but in all epithelial tumors as well, including such as are originally descended from cylindric epithelium. If their cellular elements undergo extensive anaplasia, these tumors may fall a prey to partial cornification, and the phenomenon, therefore, by no means indicates that the neoplasm is derived from horny epithelium. Cornification may also occur in metastatic growths derived from epithelial tumors, even when the parent tumor does not present any horny change.

The process is always preceded by total or at least partial death of the cells. Minute, angular, homogeneous granules of different sizes first appear in the cells; with hematoxylin these granules take a dark-blue or violet stain (Plate 72, Figs. 1 and 2). This substance is known as *keratohyalin*. The granules often occupy the greater portion of the cell, sparing only the nucleus; or the latter may be surrounded by a bright areola free from granules. Later the nucleus also undergoes changes identical with the process of pyknosis, karyorrhexis, and karyolysis. The keratohyaline granules themselves also undergo a further transformation, which is partly morphologic and partly chemic. The reaction to hematoxylin stain is lost, and in its stead there is observed a pronounced tingibility with the alkaline anilin dyes, especially Gram's method with gentian-violet and iodin-potassium iodid, which gives excellent results. The granules coalesce to form large angular splinters, while the nucleus in some cases is still preserved; later the nucleus is destroyed, the cell is loaded more and more, and finally completely filled with the constantly increasing keratin substance, except at the periphery, where a pale border usually remains permanently free. At the same time the cells usually undergo great shrinking, and by reciprocal pressure become flattened and attenuated and resemble scales. Quite commonly the cells take on a concentric arrangement like the layers of an onion, and the familiar, pearly structures or pearly bodies, which are often called *cancroid pearls*, but also occur in benign epitheliomata, are produced. The reciprocal flattening of the cells is not to be regarded as the cause or forerunner of cornification, since cornification may occur in cells that are not in the least flattened; on the other hand, these laminated structures and pearly bodies may be entirely free from any horny change.

Many of the degenerations that occur in tumors are accompanied by the formation of complex bodies of homogeneous appearance. These homologous substances, for the most part, have not as yet been investigated sufficiently chemically. They are sometimes described as *hyaline* and sometimes as *colloid* substances. *Amyloid* and *myxomatous* (or mucoid) degeneration also belongs to this category. Again we must distinguish between degenerations which take place in true tumor-cells or tumor-parenchyma and those which attack the supporting structure, the stroma and the blood-vessels. These substances also occur in tumors not only as the products of degeneration of portions of the tumor, but also as excretory products of organoid neoplasms.

Hyaline bodies, as has just been explained, often occur in the form of small, drop-like deposits between the cells; but in addition large portions of tumors, especially of the stroma, may be converted into ramifying, pellucid, hyaline cords and bands, forming a large- or small-meshed network or merely a system of cleft-like cavities which lodge the surviving cells (Plate 56, Fig. 2; Plate 78, Fig. 2—*cylindroma*). Not infrequently the walls of the blood-vessels are the seat and point of origin of extensive hyaline deposits; sometimes the hyaline substance presents a faint parallel striation. Genuine *colloid formation*—*i. e.,* the formation of a tenacious, glue-like substance, characterized by its perfectly homogeneous appearance and chemically by the fact that it does not coagulate to form threads on the addition of alcohol and acetic acid—is comparatively rare in tumors, being practically confined to enlargements and neoplasms of the thyroid gland (colloid goiter) and of the hypophysis. In these instances its formation is confined to increased secretion and the conversion of epithelial cells into colloid substance, and does not occur in the interstitial tissue.

Mucoid degeneration, on the other hand, is a wide-spread and frequent process in tumors. (Tumors that have undergone mucoid degeneration are often erroneously described as colloid tumors, especially mucoid cancers; it is desirable to reserve the term mucous or gelatinous degeneration for processes the products of which coagulate in the well-known stringy manner on the addition of alcohol and acetic acid, and which are stained a light or dark blue with hematoxylin, according to their degree of density.) Excessive production of mucus occurs especially in tumors of the ovaries and of the intestine. In the cystic tumors of the ovaries (Plate 14, Fig. 2) the formation of innumerable goblet-cells can be followed distinctly; the cells balloon on account of the accumulation of paraplasmatic cell-contents, and later burst and collapse, discharging their contents in globular masses and drops toward the lumen. The same variety of mucoid degeneration by the formation of goblet-cells can usually be observed in cancers of the stomach and intestine (Plate 14, Fig. 1), while in other so-called mucoid cancers, as in the mammary gland, for instance, the mucin is deposited in the epitelial cells in the form of single, discrete, globular masses. In addition to this mucus formation from epithelial cells a conversion of the connective substance into mucus quite frequently occurs. The process may attack fibromata to a greater or less degree; the fibers are forced apart by the mucoid masses, and the cells take on a branching or stellate shape, producing the so-called *myxomatous* tissue, which has its physiologic prototype in Wharton's jelly of the umbilical cord. Thus it is not uncommon to find a soft, fibrous nasal polypus in a state of myxomatous degeneration associated with mucus-production and retention in the glandular portions of the tumor. Myxomatous degeneration of the interstitial substance is also observed quite frequently in sarcoma (*sarcoma myxomatosum*). The ground-substance of chondroma may undergo myxomatous degeneration, and finally, even in organoid tumors, such as carcinomata, the process may be confined largely to the stroma and lead to the production of wide, soft trabeculæ between the remains of cells which coagulate in acetic acid. The starting-point of this form of myxomatous degeneration appears in the last instance to be the cement-substance between the cells or their fibers, which, on the addition of water, swells and is converted into jelly.

A rare form of degeneration in tumors is *amyloid degeneration*, which occurs only in connective-tissue tumors (fibromata, chondromata) and begins in the blood-vessels and in the stroma, but may also attack the tumor-cells. Hyaline degeneration is often observed as the forerunner of the amyloid change.

Glycogen, finally, is sometimes found deposited in tumors. The substance occurs in the form of large or small drops or crescentic masses in the protoplasm of the cells, and, more rarely, diffused through the tumor. Sometimes the cells may be completely covered with these droplets, which sometime occur in the gaps of the tissue —*i.e.*, between the cells; in the stroma of tumors glycogen is extremely rare; the nuclei of the cells always escape. Glycogen gives a specific reaction with potassium iodid, which stains it a deep brown or brownish red; in contradistinction to amyloid, however, it is not stained blue by the addition of sulphuric acid, and it gives negative results with the other amyloid reactions (compare p. 70). The granules of glycogen are usually quite soluble in water, hence only perfectly fresh preparations or such as have been rapidly hardened in absolute alcohol are suitable for examination. In contradistinction to amyloid, glycogenic deposits are speedily dissolved by the addition of saliva. The substance is probably derived from the blood. It is seen in carcinomata, endotheliomata, sarcomata (especially of the salivary glands and of the kidneys), in cysts of the ovaries and vagina, in enchondromata, rhabdomyomata, and especially in many tumors of the testicles.

CONNECTIVE-TISSUE TUMORS.

Fibroma.

The term fibroma is applied to a tumor which is composed of fully formed (mature) connective tissue. A number of different kinds of connective tissue are distinguished in the normal organs of the body, and as any one of these varieties may become the starting-point of a fibroma, it follows that the macroscopic and especially the microscopic structure of this class of tumors presents a great many varieties. The metaplasia to which connective tissue is subject gives rise to the formation of mixed and transitional forms, and, owing to the fact that other tumors may take part in the neoplastic process at the same time, combinations with other tumors may be produced, and as all these forms are included among the fibromata, this class contains a great number of different varieties.

It appears to me wise to adopt Borst's proposal to indicate the formation of complicated composite tumors in general by adding a qualifying adjective to the name of the basal form of the tumor used as a noun, and to describe the tumors formed by a combination of neoplasms of different species of tissue by the use of two coördinate nouns. According to this method we should, therefore, in a given case speak of a "*fibroma ossificans*," for example, if it appeared that a metamorphosis of connective tissue into osseous tissue had taken place within the tumor; and, on the other hand, we should use the term "fibromyxoma" to describe a growth resulting from the simultaneous new formation of connective tissue and mucoid tissue. The emphasis would be laid on whichever kind of tissue was chiefly concerned in the make-up of the tumor.

Simple fibromata—*i.e.*, tumors the parenchyma of which consists exclusively of connective tissue—have from time immemorial been divided into hard and soft. The differences in the consistence may be due not only to differences

PLATE 43.

FIG. 1.—**Hard Fibroma (Cicatricial Keloid) from the Skin of the Arm** (Hemat.-eosin. × 80.): 1, Concentrically striated fibrous tissue; 2, narrow blood-vessels between the connective-tissue fibers.

FIG. 2.—**Fibroma from the Cheek** (× 350.): 1, Narrow spindle-cell nuclei scattered through an abundant fibrous tissue which presents a parallel arrangement of the fibers; 2, thin-walled vessels.

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in the nature of the connective tissue, but to other factors, especially quantitative and qualitative changes in vascularization; for it is obvious that a piece of tissue which is supplied by numerous or by wide blood- and lymph-channels is necessarily much softer than one containing only a few vessels of small caliber.

As connective tissue is found practically everywhere in the body, the distribution of fibroma is, of course, almost universal. The site of origin has a distinct influence on their outward form; a fibroma formed in the center of a compact organ, as a rule, tends to assume a spheric shape, while a fibroma growing toward the surface of the body or into the lumen of a hollow organ tends to form a bulging prominence, or, if the growth is very active, a polypoid excrescence. The same tendency is observed in many other tumors. In the former case the surrounding tissue is often crowded to one side, and, if the pressure increases rapidly, may present pressure-symptoms, either in the form of atrophy, or, if the vessels are occluded, in the form of retrograde metamorphosis (necrosis, fatty degeneration). The growth of these tumors is usually characterized by a distinct expansive quality. The nodule enlarges from the center like a distending rubber balloon; although at times the process is somewhat more active in the outer portions of the tumor, when the periphery may throw out processes directly into the surrounding tissue. But we never observe a direct accretion of the tumor-elements by contiguity, so to speak,—*i.e.*, by the inclusion in the tumor-mass of preëxisting connective tissue from the surrounding *ing tissue*,—what might be described as a process of

Tab.43

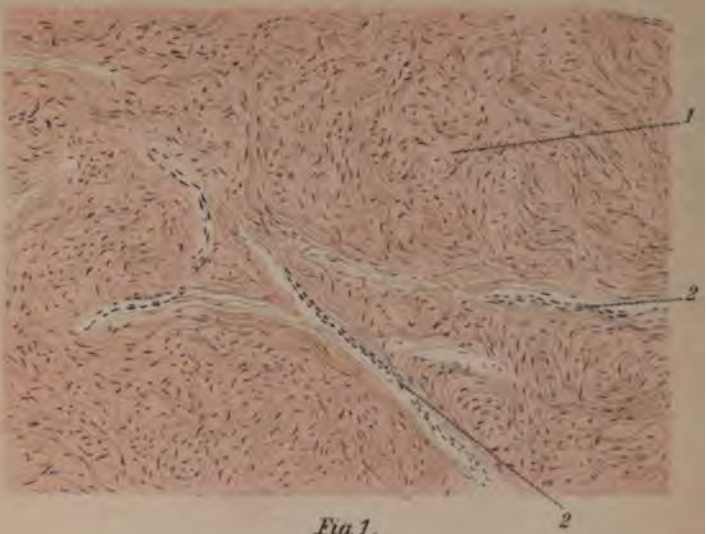
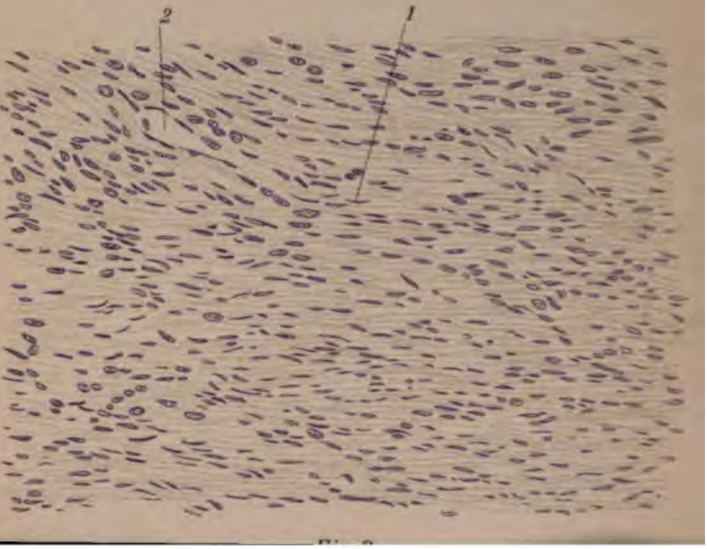


Fig. 1.



adaptation of the surrounding tissue. On the contrary, the injurious consequences which may occur from the presence of a tumor in the affected organ affect the supporting tissue quite as much as the parenchyma.

On the other hand, when a fibrous tumor grows toward the outer or inner surface of an organ, as, for example, in the skin toward its free surface, in the stomach toward its lumen, it will cause a bulging of the covering, and, as rupture practically never occurs, the surface of the advancing mass of connective tissue will be completely covered by this tissue. So long as the tumor retains its simple spheric or ovoid form the outline of the investing skin or mucous membrane will also be quite simple; but when the body of the tumor begins to throw out processes or spines from its surface or forms dendritic ramifications, the epithelium which is raised from its normal level by the growth of the tumor will be forced to follow all the depressions and elevations of the underlying tissue, and will thus be thrown into folds or made to form invaginations—in short, the layers of the skin or mucous membrane must undergo a superficial increase, which, of course, can be effected only by active increase of the cells. The same thing occurs when a connective-tissue tumor grows secondarily into an already existing hollow epithelial structure, as occurs frequently in certain forms of tumors, especially of the ovary (papillary adenoma) and of the mammary gland (intracanalicular and pericanalicular adenofibroma). In this case the new formation of another kind of tissue becomes associated with a simple connective-tissue proliferation, and the result of these two different kinds of cell-production going on *parri passu* is the production of so-called "*fibro-epithelial tumors*," which might just as well be included among the fibromata as among the epithelial tumors, but in obedience to universal custom shall be more accurately described among the latter.

The **hard fibroma** consists principally of connective-tissue fibrils, collected into bundles in a wavy, more or less tortuous arrangement, and sometimes concentrically

PLATE 44.

FIG. 1.—**Fibrous Polyp from the Nose** (Picrocarmin. × 280.): 1, Superficial epithelium arranged in several layers; 2, fibrous tissue; 3, large nuclei of shorter spindle-cells; 4, narrow nuclei from the fibrous tissue.

FIG. 2.—**Mucous Polyp from the Nose** (Hemat.-eosin. × 92.): 1, Cylindric surface epithelium; 2, loose-meshed, reticular ground-tissue; 3, mucous glands in transverse section.

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disposed within individual nodules. As a rule, the fibers are quite long. In the intervals between the fibers are the so-called connective-tissue corpuscles—*i. e.*, small, short, spindle-shaped nuclei, appearing circular in transverse section, which, as a rule, do not show any nucleolin, even under high magnification, the chromatin being practically uniform in density throughout. As a rule, no cell-bodies can be demonstrated around the nuclei, which are in close contact with the fibers; their number varies even with small sections of the same tumor. While some portions of the tumor consist almost exclusively of fibers with very few nuclei, even a low power will reveal here and there darker areas where more numerous spindle-shaped nuclei are closely packed together. On more careful examination it is then usually found that these accumulations of nuclei surround a narrow, thin-walled vessel and sometimes the fibers also present a distinct concentric arrangement around the central vessels, the turns and reflections of which are surrounded by the accompanying fibers, and a so-called "*plexiform fibroma*" is formed by the interlacing of the individual bundle systems. In the multiple fibromata which occur so frequently in the cutis and in the subcutaneous tissue similar relations with the nerve-fibers (which are usually unmedullated) are demonstrable, the proliferation beginning in the connective-tissue covering of the nerve (*neurofibroma*). The delicate connective-tissue capsules of the sebaceous and sweat-glands in the skin may also form the matrix of multiple fibroma, which may also originate in tendons, in intramuscular connective tissue, and in periosteum; other

Tab.44.

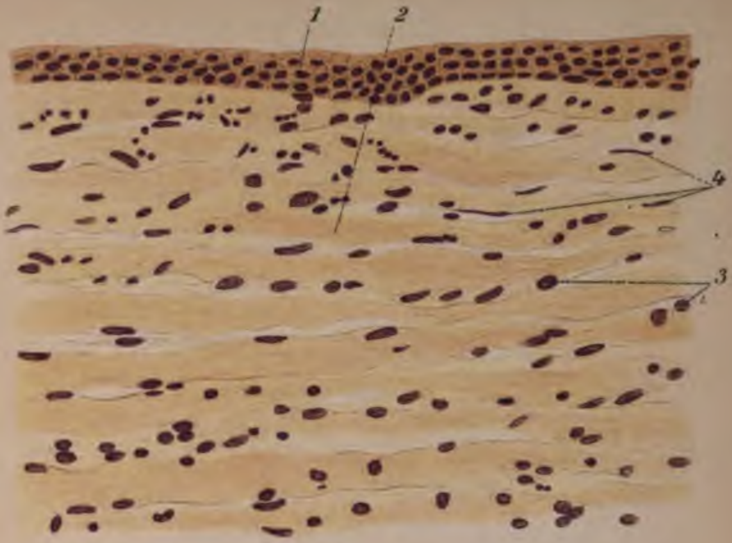

Fig.1.

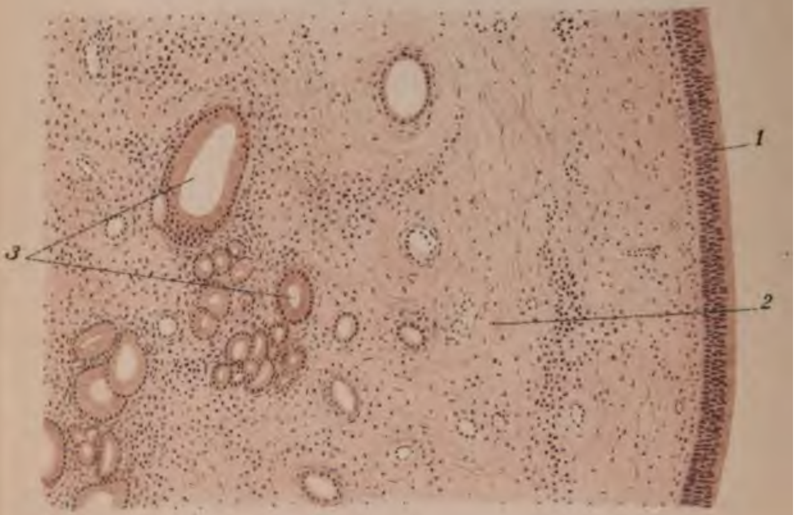

Fig.2

sites of predilection for their development are the uterus, the mammary gland, and the kidney. In the kidney large numbers of small fibromata are often found in the cortical and in the medullary substance, especially at the bases of the pyramids, but the tumors, as a rule, do not attain a large size. Seen with the naked eye, they may give rise to confusion with miliary tubercles, from which they are distinguished by their greater hardness. All these hard fibromata of simple structure are also designated "*desmoids*."

A special form of the hard fibroma in the cutaneous tissue is known as **keloid** (Plate 43, Fig. 1). It usually develops after an injury (incised wound or burn) in the form of "cicatricial keloid" by excessive scar-formation, and sometimes without any such cause, as "spontaneous keloid." It is distinguished by the dense aggregation of its fibers and the dense character of the bundles. (It is worth noting that many authors have observed a disposition for the development of these keloids to run in families). [Keloids seem to be relatively common in the American negro.—Ed.].

Many hard fibromata have a tendency to undergo retrograde metamorphosis, especially calcification. When this occurs, the fibers and bundles, which usually lose their nuclei, become completely fused in considerable portions of the tumor, and converted into uniform glistening hyaline material, which at first is distinguished by its extraordinary reluctance to take even acid anilin stains. Later a deposition of calcium phosphate and calcium carbonate in minute particles takes place, and these coalesce to form larger calcareous deposits in the shape of irregular lumps or cylindric masses. Even large tumors, the size of an infant's head and larger (especially in the uterus), may in this way be converted into compact structures of stony hardness. If any cells or nuclei survive after the beginning of calcification, they may be included in the zone of calcification; and if they are arranged concentrically around blood-vessels, they may, by simulating Haversian canals, cause confusion with true

FIGURE XI.

From a Soft, Myxomatous Fibroma of the Nasal Mucous Membrane. (Stellate connective-tissue cells, joined together with protoplasmic processes; the intercellular substance has become myxomatous and contains abundant masses of leukocytes.)

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bone-formation, as they closely resemble bone-corpuscles, although it is, of course, impossible to demonstrate any processes (*petrifying fibroma*).

On the other hand, the actual metaplasia into genuine bone-substance, with the conversion of bundles of fibers into Haversian lamellæ and the inclusion of cells, and their conversion into bone-corpuscles with well-developed cellular processes, may occur in fibromata (*ossifying fibroma, fibroma ossificans*). These forms are not to be confused with those in which a formation of bony substance is present from the beginning along with the new formation of connective tissue (*osteofibroma*).

Soft fibromata are distinguished from hard fibromata by a less robust development of the fibrous substance. The fact that they contain more tissue-juice may alone account for their softer consistence. The tissue of an originally hard fibroma may become edematous from passive congestion; the bundles of fibers are forced apart by the collection of fluid between them, clefts are formed (Plate 44, Fig. 1), and the cells and fibers enlarge by maceration. At the same time a metaplasia into true mucous tissue may take place (*fibroma myxomatodes*), the cells becoming stellate and branched, and the intervals between the processes being filled up with a mucin-containing substance which is coagulated by acetic acid.

In the soft varieties the connective tissue presents a more or less areolar structure, with shorter, more loosely arranged fibers and a greater diversity of the cells. Among the short, fixed spindle-cells some polygonal elements well provided with plasma, and circular or oval cells with dark, dense, circular nuclei suggesting lymphocytes are found. They are the so-called "wandering cells" of the connective tissue; the cell-body is sometimes completely filled

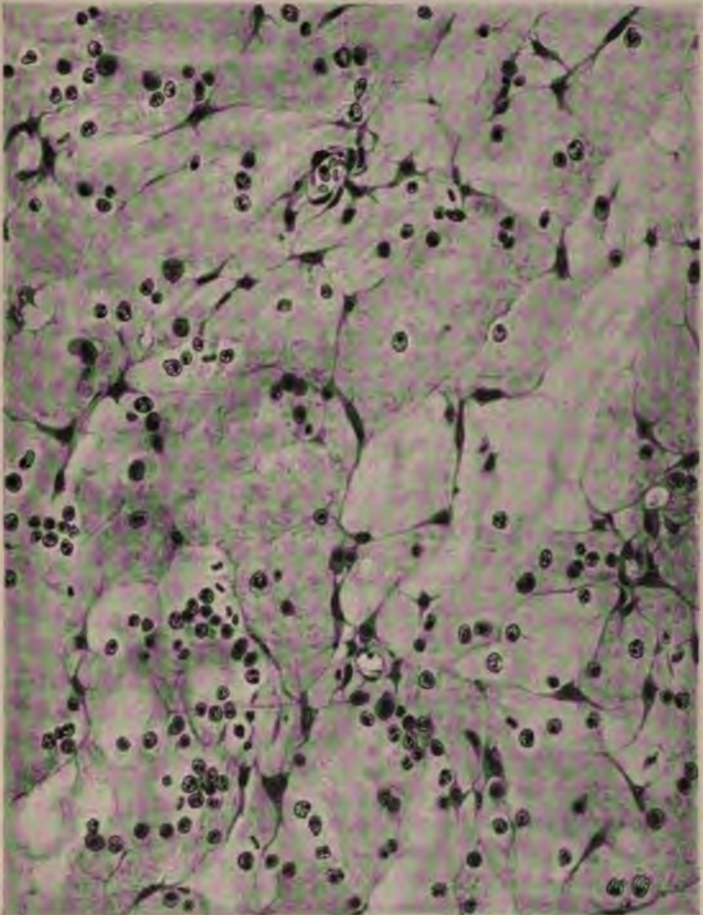

Fig. XI.

with innumerable granules which stain with eosin ("eosinophile cells"); in addition, leukocytes with fragmented nuclei are also found scattered through the tissue in variable numbers. These varieties of fibroma usually begin in a connective-tissue matrix which is normally loose-meshed and rich in cells; thus the majority of "*polyps*" found in the upper air-passages, in the gastro-intestinal canal, and in the uterus present this structure. As their development is usually associated with protracted chronic inflammatory conditions, the greater number and variety of cells that they contain are at once explained. As they grow out from the submucosa or the *stratum proprium* they push the epithelium before them and are completely invested by it, unless some secondary inflammatory process or pressure-necrosis destroys the epithelium. Thus the exceedingly common nasal polypi are covered with several layers of cylindric epithelium in which even the cilia are sometimes demonstrable. The epithelial investment may also undergo some secondary metaplasia and may become low and flat. As the polypoid structure rises above the level of the surrounding mucous membrane, glandular constituents are necessarily included in its mass; these glandular constituents may grow actively, and in this way glands sometimes develop within the polypus and project far beyond the normal mucous membrane (*glandular polypus*, *fibro-adenoma*). Not infrequently the glands included in the neoplasm are distinguished by their special tendency to the formation of goblet-cells and the accumulation of large quantities of mucus; the lumen of the glands becomes dilated, and the ducts occluded by displacement or kinking of the canal. In this way large cystic cavities containing in their interior concentrically arranged masses of mucus and desquamated and swollen epithelial cells are produced ("*cystic polyp*" and "*cystic fibroma*"). In the uterus especially these cystic polypi often attain a respectable size and the original fibrous ground-tissue, the true tumor body, is gradually overshadowed by the epithelial structures and their excretory products.

Owing to the great looseness of their parenchyma soft fibromata are, as a rule, much more richly supplied with blood-vessels than the harder tumors. The vascular development, especially in tumors of the polypoid variety, may attain an excessive degree which may reveal itself even macroscopically by the softness of the tumor and its dark-red discoloration (so-called "*raspberry polypus*"). The blood-vessels are greatly dilated, and their cells present an atypical structure, being extraordinarily thin; in fact, mere tubes of endothelium; or the continuous endothelial lining is absent altogether, and the blood courses through irregular cavernous spaces, giving the tumor an erectile character (*fibroma angiomatodes, cavernosum, telangiectaticum*). The natural results of the insufficient development of the walls are laceration of the vessel and extravasations of blood either into the tumor or into the surrounding tissue. Especially in the uterus and sometimes in the nose and in the stomach these vascular polypi give rise to considerable hemorrhages.

Some varieties of "nevus," which are to be described more fully later, ought, in view of their histology, to be included among these telangiectatic fibromata ("*nævus vasculosus*) (see Plate 49, Figs. 1 and 2).

If, as happens in rare cases, the lymph-vessels in a fibroma undergo an excessive development in number and size, the tumor is called a *lymphangiectatic fibroma*. When this form of tumor is diffuse, it leads to so-called "*elephantiasis*," in which the new formation of fibrous tissue combined with the extraordinary development of large lymph-vessels, some lined with high, almost cuboid endothelial cells, usually involves an entire limb, especially the lower extremities or the external genitalia. In this condition also chronic repeated inflammatory processes, especially relapsing erysipelas, appear to cause connective-tissue proliferation.

Finally, the **combination forms** of fibroma with other tumors must be mentioned. Not infrequently fibromata after the type of the variety with a poor cellular development present fatty cells, both in the central and in the peripheral portions of the tumor. Here we must distinguish between a metaplastic form and a true mixed form. The former is produced by gradual partial conversion of the connective-tissue cells into fat-cells by exactly the same process as in the formation of normal fatty tissue—*i. e.*, the cell-body of a connective-tissue cell becomes swollen and the seat of fat-droplets, which coalesce and form a larger drop until the original protoplasm is reduced to a delicate, membranous border and the nucleus is crowded to the wall. This represents a true fatty infiltration of a fibroma, and, according to the principles laid down above, should be designated a "*fibroma lipomatodes*," to distinguish it from a true "*fibrolipoma*," which is formed by the simultaneous proliferation of fatty tissue and new formation of connective tissue. The above-mentioned renal fibromata, which are frequently multiple, often present at their center a metaplastic fat-formation.

The combination of fibroma with the development of muscle tumors, especially in the uterus, the *fibromyoma* or *myofibroma*, is generally familiar. These neoplasms often attain a collossal size, and their structure, so far as the muscular elements are concerned, calls for further study. The combination with epithelial neoplasms, the so-called *papillomata* and *adenofibromata*, has already been mentioned. They will be described more fully with the group of fibro-epithelial tumors.

It is not altogether easy, in a histologic sense, to make a sharp division between fibroma and sarcoma. The soft fibromata especially, as we have seen, exhibit a certain variability in their cellular elements which is enhanced by metaplastic processes or by the association of other kinds of tissue in the tumor-formation. But in every case the elements represent fully formed, mature tissue, and the individual kinds of cells are uniform in shape as well as in other respects. But when the tumor begins to assume an atypical character, the process of differentiation and the greater individuality of the cells at once become evident in the appearance of a great variety of forms which indicate an arrest at a younger, indifferent stage of development, and, as regards their size, the shape of the body, outline, and chromatin contents of the nuclei, present considerable differences among one another. It is only when this atypical growth of the tumor is quite evident that the term "fibrosarcoma" is justifiable (Plate 52, Figs. 1 and 2; Plate 53, Fig. 1).

Myxoma.

The myxoma is composed exclusively of mucoid tissue, such as occurs only in the fetal organism as the forerunner of connective and fatty tissue and at the time of birth is found solely in the umbilical cord in the form of Wharton's jelly. For this reason many authors do not include the myxoma among the typical tumor-formations.

It has been shown that the metaplastic production of mucoid tissue is not infrequently observed in fibroma; it is equally frequent in lipoma and chrondroma (fibroma, lipoma, chondroma myxomatodes). The process consists in a disappearance of the ground-substance of these tumors—*i.e.*, of the fibers, fat, or hyaline, cartilaginous substance, and its replacement by a mucoid or gelatinous, semifluid mass which is coagulated by acetic acid. (It has been pointed out previously that a simple edematous swelling of connective tissue is not to be confounded with the formation of myxomatous tissue.) The cells at the same time suffer a material change of shape; they swell up, their protoplasmic bodies become polygonal and usually granular, and send out multiple or forked and branching processes, which interlace and form a felt-like network, within the meshes of which the mucous ground-substance is suspended.

Exactly the same structure is observed from the beginning throughout the tumor in the much more uncommon pure myxoma. The spindle-shaped, stellate, or spider-like cells with their numerous processes are best isolated in recent, teased preparations, the typical structure being more difficult to recognize, and the multiple processes are also less distinct in hardened sections on account of the great loss of water from the soft tissue. This loose, soft tissue is usually traversed by bundles and septa of somewhat denser fibrous tissue for the accommodation of the blood-vessels, which are often well developed. Leukocytes in variable numbers are found scattered throughout. Not infrequently minute fat-droplets are seen in the protoplasm of the cells and at the base of their processes.

A combination of proliferation of myxomatous tissue with new formation of other kinds of tissue is, on the whole, more frequent than a simple myxoma. Streaks of myxomatous tissue are observed in many so-called *mixed tumors*, particularly those which occur in the parotid gland and in the testicles. In these situations the myxoma occurs in connection with fibromatous foci, cartilaginous and osseous tissue, and occasionally epithelial formations or cystic structures (Fig. XXXVI.).

Like fibroma, pure myxoma sometimes develops in a multiple form along the course of nerves (so-called "*neuromyxoma*"). Myxomata also occur in periosteum, in the cutis, in the heart, in the marrow of bone, and, especially in the new-born, in the mesentery, where they occasionally form extensive gelatinous tumors which protrude from the abdomen as soon as it is opened.

When the cells of a myxoma are numerous, closely packed, and polymorphous, the tumor is spoken of as a *myxosarcoma*, and it is probable that the combination of the two varieties of tumors was present from the beginning. It is needless to say that secondary conversion into mucoid tissue by softening and the deposition of a gelatinous, mucoid substance may occur in a sarcoma ("*sarcoma myxomatosum*").

The myxosarcomata are usually distinguished by the formation of very large polynuclear cells.

Lipoma.

The term "lipoma" is applied to a tumor consisting exclusively of fatty tissue. Histologically, it does not present any essential difference from the structure of the panniculus adiposus, nor is it always quite easy to define the boundary between a circumscribed adiposity and tumor-formation—for example, in so-called Madelung's fatty neck (*lipoma annulare colli*). But in most cases the lipoma is a distinctly circumscribed tumor of extremely variable size. Usually lipoma is primarily due to the proliferation of preëxisting fatty tissue in the subcutaneous, subserous, subsynovial, intramuscular connective tissue, or in the mammary gland; more rarely lipoma develops in organs which do not normally contain fat (aside from the hilus and capsule)—*e.g.*, in the meninges, in the larynx, and even in the liver. Such cases suggest an anlage for the tumor from the dissemination of germs of fatty tissue during fetal life, unless one chooses to assume a metaplastic formation by the deposition of fat in original fibrous tumors.

Sometimes growing lipoma presents, in addition to typical, fully formed fat-cells, which may be extremely variable in size, young fat-cells, circular or oval in structure, with one or more nuclei and an extensive protoplasm, containing a few scattering fat-droplets. The vascularization of lipoma is usually quite abundant; the larger arterial and venous trunks are carried in connective-tissue septa between the individual clusters of fat, and send out smaller branches between the cells. Occasionally telangiectatic areas develop, especially in pedunculated lipoma of the skin.

Lipoma is subject to a variety of retrograde metamorphoses which sometimes obscure the original texture of the tumor and render it quite unrecognizable. Thus, the fat-cells may undergo complete colliquation, with dissolution of their nuclei and disappearance of the connective-tissue envelops and septa of the individual clusters. The lipoma, or a part of it, is thus converted into a cystic cavity filled with an oleaginous mass. Mucoid softening of lipoma is also observed in rare cases; a mucoid, stringy substance is deposited in the intervals between the fat-cells; more rarely a true conversion of the fat-cells into *stellate*, myxomatous cells embedded in a mucoid ground-substance takes place (*lipoma myxomatodes*). On the other hand, a lipoma may become indurated either by progressive increase in the fibrous intercellular substance and consequent fibrous metamorphosis (*lipoma durum*), or by the deposition of calcium salts. In the initial stages the cell-bodies, especially in the peripheral cells of the clusters, are filled with needles of fatty acids, in combination with calcium, presenting a brush-like or radiating arrangement, and later the entire tumor may be converted into a dry, mortar-like, or chalky mass (*lipoma petrificans*).

Combinations of lipoma with other forms of tumor are also quite frequent. Especially in multiple lipoma of the skin, as in the case of the analogous multiple fibroma, it is possible to demonstrate some connection with the nerves, which also reveals itself quite clearly in the clinical phenomena caused by these tumors [adipositas dolorosa.—Ed.]. Such lipomas sometimes contain numerous nerve fibers; but whether they are newly formed fibers or, what is more likely, whether the lipoma has formed in their connective-tissue sheaths (so-called *neurolipoma*), is an open question. Fatty tissue is also found in the teratoid mixed tumors.

Chondroma.

Chondroma is a tumor consisting of cartilaginous tissue. In most cases it takes its origin in preëxisting cartilage. When, for example, a small cartilaginous outgrowth forms in the articular cartilages, it is known as an ecchondrosis; but when cartilage forms on the surface of parts of the skeleton and exhibits an independent, tumor-like character, the term "ecchondroma" is used. When a cartilaginous tumor originates in the marrow of bones, it is called enchondroma.

Microscopically, chondroma resembles hyaline cartilage more than any other variety; but occasionally the picture of fibrous or reticular cartilage may be produced.

The parenchyma of a chondroma usually consists of cells enclosed in a hyaline ground-substance. The latter may present great variety as regards density; even in a

PLATE 45.

FIG. 1.—**Chondroma from the Lungs** (Hemat.-eosin. × 65.): 1, Hyaline cartilaginous substance with distinct lacunæ; 2, denser accumulation of connective tissue.

FIG. 2.—**Chondroma from the Parotid Gland** (Hemat.-eosin. × 280.): 1, Hyaline ground-substance; 2, cartillage-cells; 3, multiple cartilage-cells in a single cavity; 4, calcified capsules of lacunæ.

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small section of the same tumor compact portions, poor in cells and usually presenting a darker stain than the neighboring tissue, alternate with paler and more loosely arranged cells. In the first place, the compactness with which they are arranged is extremely variable. The cells may be so abundant and so closely packed as to leave only narrow bridges of ground-substance; the arrangement of cells may thus remind one of the picture of a large-celled cartilage, sometimes even of the cartilage columns in normal ossification, and there may be a certain regularity in the position of the cells. As a rule, however, they are scattered through the ground-substance with apparently no attempt at regularity, and they may be so scanty that broad, hyaline islands and bridges remain between them. The form and size of the cells are also subject to considerable variations. They are most frequently circular or oval, and have a small vesicular nucleus, although in the outer layers of the tumor or tumor-lobes spindle-shaped elements, reminding one of connective-tissue cells, and irregular, dentate forms also occur. Sometimes they contain more than one nucleus. The cells are usually surrounded by a distinct capsule; sometimes two, three, or even more cells are found within one capsule. The line of separation between the capsule and the surrounding hyaline ground-substance is also quite variable as regards distinctness; the density of the capsule may be extraordinarily variable, and sometimes distinctly circular rings, presenting a sharp contrast in their tinctorial qualities to the surrounding tissue, may be formed; occasionally, however, the capsules may be altogether absent and the cells may be contained in cavi-

Tab.45.

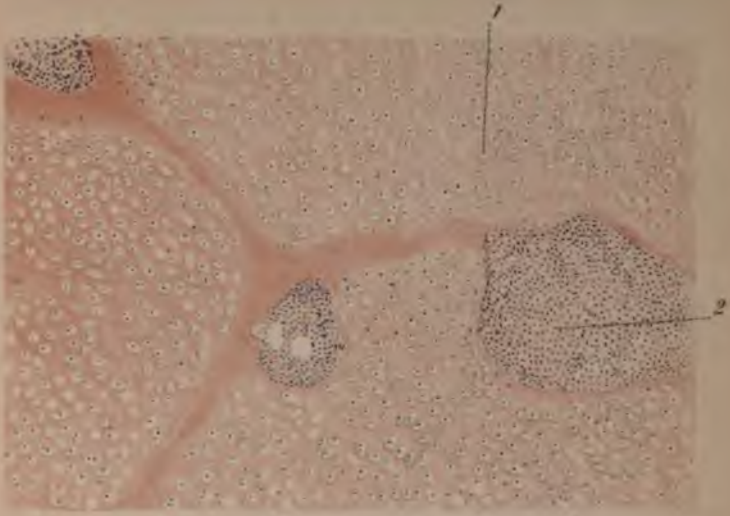
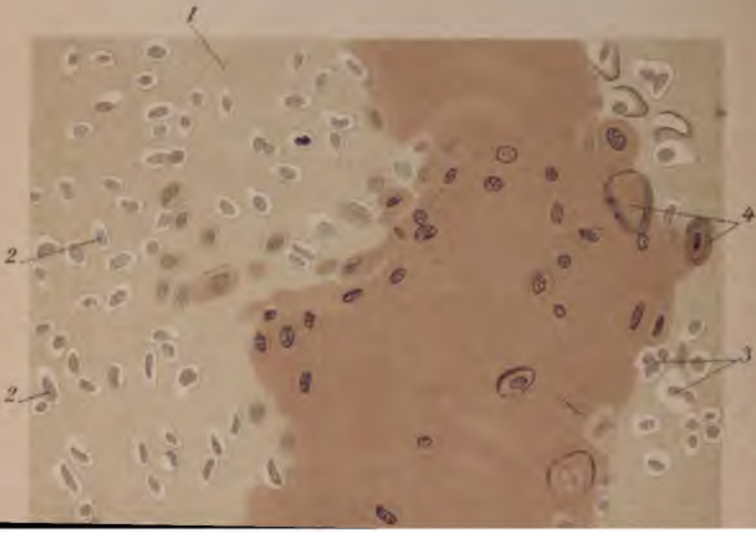


Fig.1.



ties within the ground-substance, without any attempt at delimitation. The latter condition is regulary observed in the special form of the so-called *osteoid chondroma* described by Virchow, which has usually its origin in the periosteum. It consists entirely of a homogeneous ground-substance, which is not lamellar, and exhibits a great tendency to calcification, and of cells, for the most part spindle-shaped, inclosed within the ground-substance.

As cartilaginous substance, even in tumors, is devoid of blood-vessels, chondroma as a class presents a more or less fully developed connective-tissue stroma which carries the blood-vessel and traverses the cartilaginous substance in the form of septa, inclosing circular portions of the tissue and thus giving the tumor a lobulated structure. This connective tissue, therefore, represents the perichondrium in cartilaginous tumors.

A special form of chondroma sometimes develops in the clivus of Blumenbach, protruding from the spheno-occipital suture, breaking through the dura mater, and bulging out into the cranial cavity in the form of a soft nodule the size of a cherry-stone. This tumor was designated by Virchow *ecchondrosis spheno-occipitalis physalifora*, and was attributed by H. Müller to the growth of surviving germs of the notochord, and accordingly called by Ribbert *chordoma.* It consists of large, balloon-like cells, imbedded in a hyaline substance which is usually but sparingly developed. The cells are circular in shape, possess a small, somewhat crescentic protoplasmic body and a small nucleus of great density, and contain one or more alveoli filled with fluid. (On account of its swollen appearance, resembling plant-cells, the neoplasm has received the name "*physaliformis.*") The investigations of Ribbert show that the tumor projects into the bony substance of the sphenoid and of the occipital bones, the medullary cavities of which are in part filled by the cells.

Owing to deficient vascularization of cartilaginous substance, especially in large cartilaginous tumors, retrogressive metamorphosis is, of course, exceedingly common;

FIGURE XII.

Chondroma of the Sternum (Recent Frozen Section. × 300.): 1, Hyaline ground-substance; 2, cartilage-cells; 3, lacunæ inclosing several cartilage-cells which have undergone partial fatty degeneration; 4, perichondrium.

processes of softening are particularly frequent in the cartilage. The ground-substance dissolves and is converted into a colorless, watery, or somewhat viscid fluid. At the same time the cells undergo fatty degeneration. In this way cystic cavities are formed in the interior of the tumor-nodules (*chondroma cysticum*), which at first are divided by a few remaining septa into compartments like the divisions of a fan, until finally these septa also disappear. The process is not to be confounded with softening due to metaplastic conversion into true myxomatous tissue, which also is observed not infrequently in chondroma (*chondroma myxomatodes*). This process leads to solution of the hyaline ground-substance and its conversion into a distinctly mucoid material, the nature of which is usually at once recognized by the intense blue color in preparations stained with hematoxylin. The cells lose their capsules and are converted into stellate structures with branching processes which anastomose with one another. The line of separation between this structure and the cartilaginous substance is usually very indistinct.

Calcification is frequently observed in chondroma, usually in the form of an irregular sprinkling of crumbling granules of calcium salts, so that to the naked eye the tumor in cross-section appears to be covered with whitish spots. At first the process consists of a deposition of very minute particles of lime, especially in the cell-capsules and the adjacent parts of the ground-substance. As the calcium is not, as a rule, deposited in regular circles, and gaps remain between the deposits, which in a transverse section appear triangular, with the base directed toward the cell, the histologic picture presents the greatest similarity to true bone-substance, especially when the ground-substance

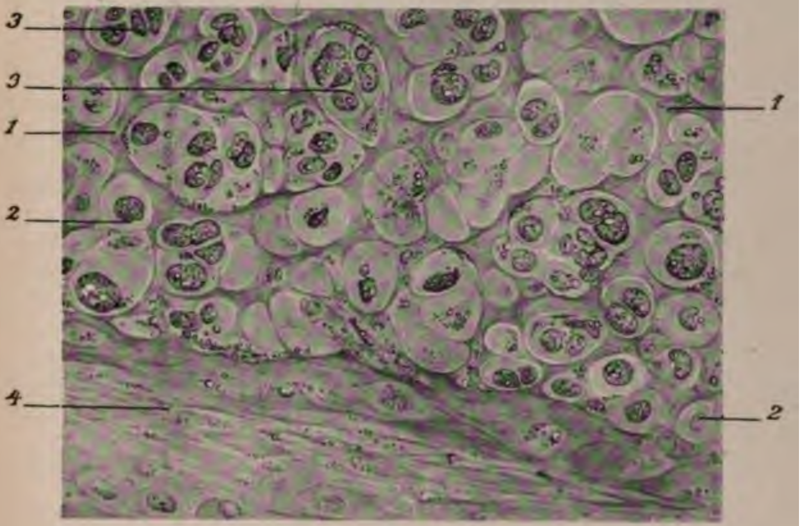


Fig. XII.

between the cells has also undergone complete calcification. After the calcium has been dissolved out with acid (gypsum reaction with sulphuric acid) it becomes evident that the process is not a true ossification, as no medullary spaces or Haversian lamellæ are found. In chondroma that has undergone complete ossification the cells are usually destroyed.

True *bone-formation* may occur in chondroma as a metaplastic process, in much the same way as in endochondral ossification. The blood-vessels contained in the connective-tissue septa first throw out processes and produce medullary spaces within the cartilaginous substance, the cellular material of which is probably furnished in part also by the liberated cartilage-cells. Then true rows of osteoblasts are formed, and this is followed by the orderly arrangement of bone-substance in contiguous layers. The process of ossification may, however, also progress by the direct calcification of the cartilaginous ground-substance and the conversion of cartilage-cells into bone-cells provided with processes.

It is probable that a displacement of cartilage in fetal or postfetal life is responsible for the formation of chondroma. Aside from genuine ecchondrosis, this variety of neoplasm is found chiefly in situations near where cartilage is normally present. In this way chondroma of the lung may be explained by the displacement of cartilaginous portions from the bronchi. Chondroma of the mamma are derived from costal cartilages, and similar tumors in the neck and in the thyroid gland from the remains of branchial canals (*branchiogenic chondroma*). The explanation of multiple chondroma that sometimes appear in the soft membranes of the brain and spinal cord is more difficult.

Scattered particles of cartilage are frequently found in the mixed tumors of the testicle, the ovaries, and the parotid gland, and in teratoma occurring in the region of the coccyx. In the case of tumors growing in postfetal life, Virchow also assumed that they were due to the dis- and displacement of cartilage-cells, especial the case of enchondroma growing from the medullary spaces; the process being assisted by the proliferation that takes place in *rickets* and the irregularities in calcification and ossification characteristic of that disease.

It has been known since time immemorial that chondromata, although they are usually counted among the so-called benign tumors, not infrequently present a tendency to form metastatic tumors, often of very alarming extent—as, for example, in the lung. This is another example of what has been said before, in the general discussion of tumors, that the histologic structure of a tumor in itself is no criterion as to whether the tumor is benign or malignant. In the case of chondromata, metastasis is either continuous or discontinuous. A continuous metastasis may sometimes cover considerable distance by continued growth in the lumen of a vein; in this way it may often extend by a continuous route into the right heart, and, skipping the right ventricle, continue to grow into the pulmonary arteries. Discontinuous metastasis also occurs from the encroachment of the primary tumor on venous trunks and the propagation of particles of the tumor by the blood current. This peculiarity is evidently due to the great power of transplantation possessed by cartilaginous tissue.

Combinations of chondroma with other tumors (*chondrofibroma*, *chondromyxoma*, *osteochondroma*) are much more frequent than the pure forms, and are produced by the simultaneous proliferation of various tissues. An important variety is *chondrosarcoma*, which will be discussed at greater length elsewhere.

Osteoma.

It is often more difficult in the case of osteoma than in the case of chondroma to make a sharp distinction between a true neoplasm and circumscribed hyperplastic processes, on the one hand, and secondary ossification in various kinds of tumors, on the other hand. With the latter we have already formed some acquaintance in connection with the discussion of fibroma and chondroma, and we shall meet them again among certain forms of sarcoma. They are due to a metaplastic formation of true bony substance in circumscribed portions of other forms of connective-tissue tumors, and it is obviously not justifiable to speak of an "osteoma," or fibro-osteoma, or chondro-osteoma in describing such tumors, which should be designated as ossifying fibroma, chondroma, etc.

Much more frequently, however, tumor-like formations of bone are observed in direct or indirect connection with parts of the skeleton, as outgrowths, so to speak, or as a circumscribed or diffuse increase in the volume of the bone, and these formations must be distinguished from true osteoma.

Diffuse thickening of bone, a condition in which the cortical layer of long, or sometimes of flat, bones is increased in all its dimensions, and a large portion of the spongy substance also is converted into compact bone by the encroachment of systems of lamellæ on the medullary spaces ("*eburnation*"), is designated *hyperostosis.* If the increase in volume is local or circumscribed, the outgrowth may be cylindric, club-shaped, papillary (wart-like), hemispheric, or tubercular—*exostosis*—or the structure of the outgrowth may be less compact, and spongy—*osteophyte.* Among the exostoses we distinguish those which are situated directly upon the bone and which are known as *continuous*, from those which are found at some distance from the bone in the adjoining soft parts, and which are known as *discontinuous* exostoses. When the exostosis is connected with the bone by a fibrous bridge derived from the periosteum, it is known as a *movable exostosis;* and when it is situated outside of the periosteum, it is called a *parosteal exostosis;* and, finally, when it is possessed of a cartilaginous investment like the articular surfaces of the epiphysis it is known as a *cartilaginous exostosis.*

These formations all result from hyperplastic or chronic inflammatory processes.

In this class also belong processes of ossification in the intramuscular connective tissue, which may result in extensive bone production and either lead to a complete

PLATE 46.

FIG. 1.—**Osteoma of the Lung** (Hemat.; bleu de Lyon. × 75.): 1, Bone-trabeculæ; 2, fibrous interspaces not presenting the characters of medullary spaces.

FIG. 2.—**Osteoma of the Thyroid Glands** (Hemat.; bleu de Lyon. × 100.): 1, Bone-trabeculæ showing distinct lamellar stratification; 2, fibrous interstitial substance; 3, large formations resembling medullary spaces.

FIGURE XIII.

Osteoma of the Dura Mater. (Thinly Ground Section. × 70.): 1, Vascular medullary spaces; 2, bone substance with lamellar stratification; 3, closely packed bone-corpuscle; 4, papillary surface of the bony formations.

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conversion of the muscle into irregular and jagged bone (*ossifying myositis*); or, when they are due to the repeated and intermittent action of pressure or of a blow (*riders' bone* and "Exercierknochen" in the abductors of the thigh and in the deltoid muscle) circumscribed masses of bone may form. Some authors (Ziegler) attribute the occurrence of these processes to a peculiar congenital predisposition.

Some of the so-called osteomata of the lungs, especially the small coral-shaped and dentate formations, must also be attributed to secondary bone-formation in connective-tissue proliferations on a chronic inflammatory base.

It is hardly necessary to state that the massive depositions of calcareous material in the form of scales or plates in the pleuræ and the pericardium which are the result of organization of exudates and often are enormously thick, forming a veritable cuirass around the heart and lungs, are not to be included among the osteomata, although they were formerly so classified. They consist simply of petrified connective tissue, which, however, when examined under the microscope, may exhibit a certain similarity to bone so long as the cells have not disappeared.

Hence, if all these "pseudo-osteomata" are excluded, the domain of the true osteoma appears much restricted.

Tab. 46.

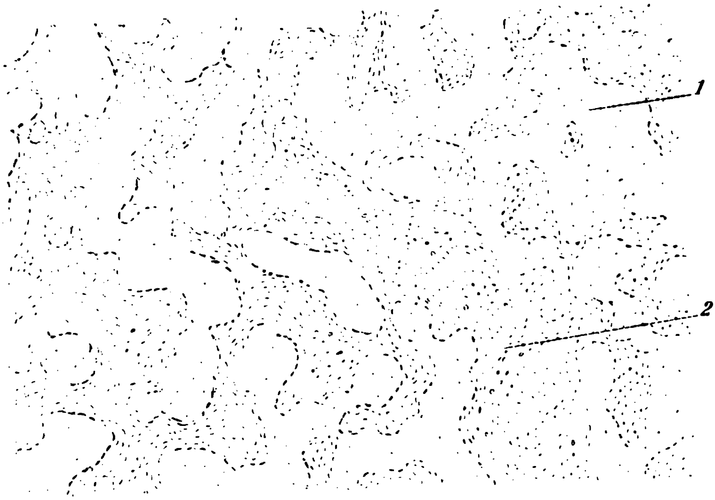
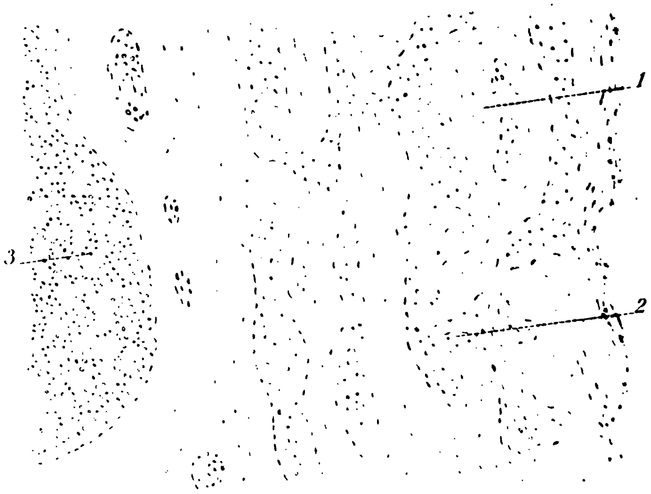


Fig. 1.



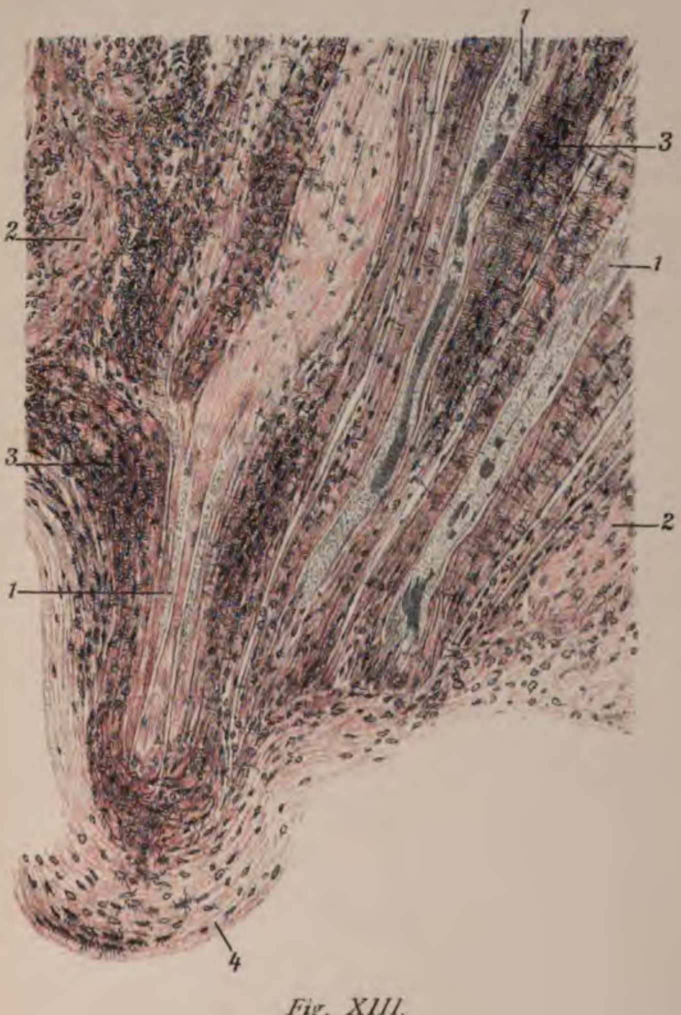


Fig. XIII.

It includes only such neoplasms as originate from the beginning in a tumor-matrix of true bone-substance. They are formed exclusively on a matrix that also produces normal bone—*i.e.*, they are either enchondral or periosteal; although it is true that the tissue which acts as the germinal layer, on account of dislocations that have occurred either during fetal or during postfetal life, often fails to show the normal relations with the skeletal system. From a histologic standpoint, then, the requirements of a true osteoma are that it shall present all the characteristics of true bone,—calcified ground-substance, typical cell-production with processes and medullary spaces. Two main forms are distinguished, depending on the density of the texture, the *compact*, and the *spongy* osteoma. The former imitates the structure of the cortical layer of the hollow bones; the ground-substance is arranged in typical lamellar systems, between what are rows of bone-corpuscles. Haversian canals are also present. Tumors of the second group contain only delicate bone-trabeculæ, like the spongy substance of the skeletal bones, and the structure is, accordingly, loose and spongy. Birch-Hirschfeld added a third variety to these two, the *medullary osteoma*, in which the medullary substance predominates.

The growth of an osteoma is effected, as in the case of normal bone, through the agency of osteoblasts arranged in rows, which first secrete ground-substance and then become included within the ground-substance in the form of bone-corpuscles. It is in the cellular material which occupies the medullar spaces that the osteoma mostly presents some deviation from the structure of normal bone. In large osteomata, as, for example, in the dura mater and most frequently in the falx cerebri, the bone-marrow may be well developed and contain typical fat-spaces. The origin of these tumors is readily explained by assuming that parts of the cranial bones have been displaced and included in the dura mater which fills the function of an internal periosteum. In the compact osteoma of the lungs also (disregarding the formation derived from the metaplasia of inflammatory products), which owe their origin chiefly to an endochondral ossification of displaced cartilage derived from the bronchial tree, we usually find a fairly well-developed bone-marrow with blood-vessels and marrow-cells. The so-called "*enostomata*," which grow in the medullary cavities of the long bones, usually exhibit a structure identical with that of normal bone; these tumors are supposed to be formed chiefly from displaced bone germs as a result of rickets.

As regards medullary substance, however, especially in the case of spongy osteoma growing in soft parts, it is frequently impossible to recognize the structure either of red or of fat-marrow, the structure being made up solely of coarse fibers (Plate 46). The scanty blood-vessels are enveloped in a more or less cellular connective tissue, which fills the medullary spaces and almost everywhere lies in immediate contact with the bone-trabeculæ. As the development of the connective tissue goes on hand-in-hand with that of the bony portion of the neoplasm, such a tumor is, strictly speaking, an *osteofibroma*. It is needless to say that this variety must be carefully distinguished from those bone-containing tumors which originally consist solely of fibrous tissue and in which the bony substance is formed by metaplasia of a part of this fibrous tissue (*fibroma ossificans*). When the connective tissue in an osteoma is particularly rich in cells and becomes arrested at an embryonal, immature stage, the term osteosarcoma is used (see below). The bony substance itself in such tumors presents some deviation from the physiologic type; the lamellar stratification disappears, and the bone-corpuscles possess no processes; at the best they are provided with capsules (*osteoid sarcoma*).

Myoma.

These tumors, which originate in muscle substance, may be composed of smooth or of transversely striated muscle-fibers. For the first variety, which is by far the more frequent, the term *leiomyoma* or *myoma lævicellulare* is used; for the secondary variety, the term *rhabdomyoma* or *myoma striocellulare*.

Leiomyoma.—Leiomyoma consists of smooth muscle-fibers arranged in bundles, nearly always interlaced and knotted, so that the tumor appears spheric and macroscopically reveals its fasicular structure in transverse section. The muscle-bundles are coiled in every direction and upon themselves like the shell of a snail, and several independent fasçicular systems can be made out as a rule; this arrangement results in the typical nodular structure, which is observed even in small myomata. Within the muscle-bundles the muscle-cells are arranged in parallel layers; in a fresh preparation, after it has been thoroughly acted upon by acetic acid, and in stained sections, the cells exhibit rod-shaped nuclei containing an abundance of chromatin and drawn up in regular array at uniform intervals from one another. These nuclei differ from connective-tissue nuclei, which are pointed at each end ("connective-tissue corpuscles"), by the fact that they are of a uniform width throughout their entire length. It is not easy to bring out the cell-bodies in stained preparations. They are so closely packed that the lines of intercellular cement-substance do not become visible without special preliminary treatment. On the other hand, they can readily be isolated in the fresh preparation by appropriate maceration, and the shape of the cells is thus well brought out.

It is needless to say that, in the microscopic preparations, the muscle-bundles are seen in longitudinal, transverse, oblique, and in a number of intermediate sections, although each group of closely aggregated cells always appears in the same sectional plane. In a thick preparation the curved ends of the fasciculi can sometimes be brought into view by focusing as they change from the longitudinal to the oblique or transverse direction. In transverse section the cells appear polyhedral, with flattened edges from mutual pressure, and a dark, round nucleus. As the cells are considerably longer than the nuclei, it is evident that, unless the nucleus happens to be included in the transverse section, there will be more sections of cells than of nuclei.

PLATE 47.

FIG. 1.—**Leiomyoma of the Uterus** (Hemat.-eosin. × 280.): 1, Muscle-cells in longitudinal section; 2, bundles of smooth muscle-cells in transverse section.

FIG. 2.—**Rhabdomyoma of the Kidney** (Picrocarmin. × 625.): 1, Muscle-fibers with distinct transverse striation; 2, spindle-shaped muscle-fibers with indistinct transverse striation; 3, irregularly shaped muscle-cells; 4, transverse sections of muscle-cells with nuclei; 5, transverse sections through parts of fibers devoid of nuclei; 6, red blood-corpuscles.

The proportion of connective-tissue in myoma is extremely variable. Macroscopically the quantity may be approximately determined by the consistence of the tumor and the amount of fluid. The more connective tissue a myoma contains, the harder and drier it will appear. On microscopic examination the strands of connective tissue appear as paler bands contrasting with the darker arears of muscle-tissue; some stains (Hansen) are especially adapted to emphasize the tinctorial difference between muscle-substance and connective tissue. The latter is frequently more dense around the blood-vessels, where it is arranged in massive layers and sends out processes of variable thickness between the bundles. Sometimes the connective tissue is so abundant that it equals in quantity or even exceeds the muscle-substance. As it must be assumed, however, that the two kinds of tissue develop simultaneously, a tumor of this kind is spoken of as a *fibromyoma* or as a *myofibroma*. Uterine myomata, and among them especially the subserous tumors, often exhibit this abundance of connective tissue.

Elastic fibers are present only in small amounts outside of the blood-vessels. The latter also present certain peculiarities in myoma. The endothelium is frequently high, and sends out projections into the lumen. Sometimes the muscular layer is abnormally developed, and in transverse section appears as an excessively broad, circular structure. Indeed, it would appear that some myomata, especially myomata of the skin, but also those which grow

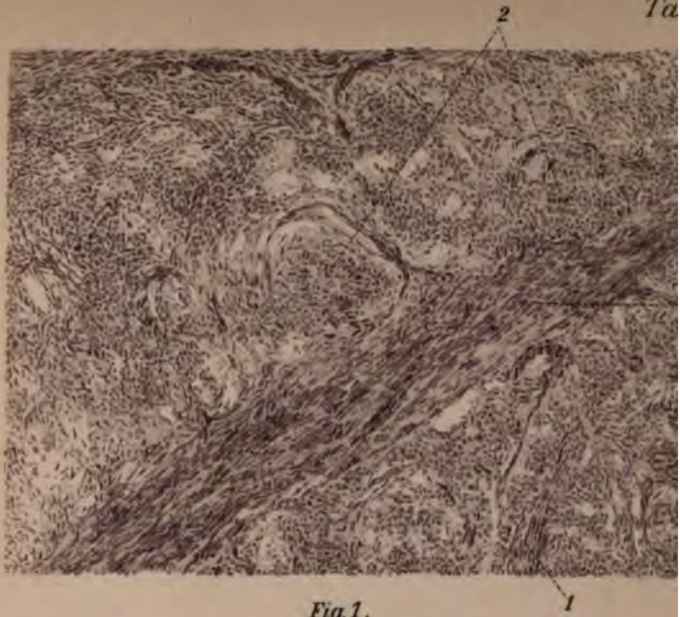
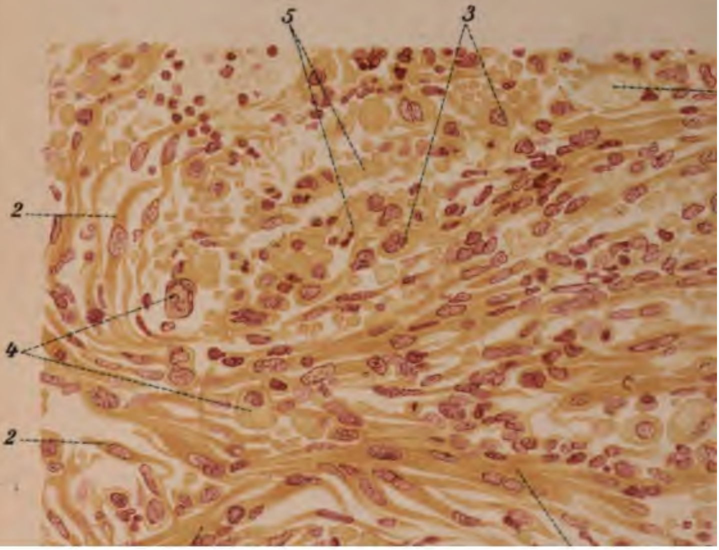


Fig. 1.



in the uterus, owe their origin to this hyperplasia of the muscular layer of the arteries; for the hyperplastic tissue is often connected by radiating fascicular processes with the bundles of the true tumor-parenchyma. The connective tissue in myoma usually contains but few migrating and round cells; sometimes mast-cells, either singly or connected in small groups, are found in the connective, as well as in the muscular, tissue.

Uterine myomata in many cases present a noteworthy peculiarity which was first pointed out by von Recklinghausen. This peculiarity consists in the inclusion of epithelial tubes and ducts, and is observed chiefly in myomata situated at the angles of the tubes. These inclusions consist of cuboid or cylindric, in rare cases ciliated, epithelial cells in immediate contact with the muscle-substance. Not infrequently several adjoining cyst-like cavities lined with epithelium are observed, or a number of closed epithelial tubes are found radiating from a main duct or projecting like the teeth of a comb. Such tumors might properly be called *adenomyomata*. Von Recklinghausen attributed these inclusions of epithelium to remains of the Wolffian body, and afterward it was proved (Klein and Groschuft) that Wolff-Gärtner's duct can sometimes be traced from the broad ligament as far as the hymen (sinus urogenitalis). An attempt has also been made to utilize these findings for the explanation of the congenital origin of myoma. Subserous uterine myoma sometimes contains cystic inclusions of epithelium derived from the peritoneal epithelium (Aschoff), and submucous myoma, in its subsequent growth, may snare off some of the uterine glands so that the latter are included within the tumor.

Myomata are subject to various forms of retrogressive metamorphosis. Softening from edematous infiltration and swelling occurs chiefly in pedunculated, subserous, and in polypoid, submucous myomata of the uterus, as the result of torsion or kinking at the point of attachment and consequent interference with the return of blood. The same conditions may lead to the production of extensive hemorrhagic infarcts in such tumors. The pedicle of a submucous myoma may be completely divided, in which case the neoplasm is at once expelled, or, being deprived of nutrition, undergoes a process of maceration manifesting itself in complete destruction of the cells, or, if putrefactive germs gain an entrance, in true putrefaction.

In rare cases isolated metaplastic processes confined to the connective tissue, such as conversion into mucous tissue, result in the formation of *myoma myxomatodes.*

Owing to deficient nutrition, softening by fatty degeneration may take place, especially at the center of a large myoma. In such tumors yellowish spots are noticeable even macroscopically in a transverse section, and the tissue in these yellowish areas is of a soft, almost semifluid consistence. The muscle-cells degenerate and are replaced by a mass of detritus consisting of innumerable small and large fat-droplets; in the immediate neighborhood minute fat-droplets are also seen imbedded in surviving muscle-cells, the nuclei of which are in various stages of disintegration. Processes associated with increase in the consistence or hardness of a tumor are still more frequent. The connective tissue becomes hard and sclerotic, the cells disappear, and a hyaline metamorphosis takes place, which sometimes attacks the muscle-tissue secondarily, and, after destroying the staining properties of the nuclei, converts the muscle-tissue also into the familiar homogeneous vitreous mass.

This process is usually a forerunner of more extensive changes, especially the deposition of calcium salts, at first in small particles beginning in a few centrally situated islands, and later in larger conglomerations forming solid incrustations and converting even large myomata into heavy masses, as hard as stone, that cannot be cut with anything but a saw.

Myoma quite frequently becomes converted into rapidly growing malignant sarcomatous tumors. It is to be assumed that the atypical cell-production in such cases begins in the connective-tissue stroma. The embryonal connective-tissue cells are produced in excessive numbers and encroach on the muscular elements so that the latter atrophy and disappear. It is conceivable that the sarcomatous degeneration might begin in the muscle-cells, and the statement that it does has been advanced by various authors; but it is altogether devoid of proof.

Leiomyoma is observed most frequently in the uterus, especially in nulliparous, middle-aged women. Any portion of the uterus may be attacked by the disease, the cervix more rarely than any other. According to the relation of the tumor to the wall of the uterus they are distinguished as subserous, intramural, and mucous myomata. Next to the uterus the favorite situations for the development of these tumors are the tube and the broad or, more rarely, the round ligament. Myoma may, however, also develop in the esophagus, stomach, and intestine, in the urinary passages, the pelvis of the kidney, the ureters and bladder, the testicles (gubernaculum Hunteri), and, finally, in the skin, where the tumors are often multiple. In the skin they sometimes grow from the muscular wall of the blood-vessels, but more frequently from the minute arrectores pilorum and the delicate layers of muscle in the sweat-glands. Cutaneous myoma often exhibits a cavernous structure from simultaneous proliferation of the blood-vessels (*angiomyoma*).

Rhabdomyoma.—Rhabdomyomata are rarely uncomplicated—that is, consist solely of transversely striated muscle-cells. As a rule, striated muscle-cells are present only in variable quantities in a ground-substance of sarcomatous tissue. As it seems probable that the latter begins to take part in the formation of the tumor at the same time as the muscle tissue, the tumor should be called properly *rhabdomyosarcoma*.

The transversely striated muscle-elements themselves rarely appear in their typical fully developed form in these tumors—that is, they are not identical with the voluntary muscle as it appears after teasing. They are arrested in their development at a comparatively low stage, and appear as quite immature structures, differing materially from the physiologic type. These forms have also been incorrectly called *rhabdomyosarcoma*, although they are not the result of a combination of rhabdomyoma with sarcoma, but at most present a rhabdomyoma of sarcomatous type—granting that the term scarcoma is admissible for structures consisting of transversely striated muscle—*i. e.*, rhabdomyoma sarcomatodes.

The tumor elements of a rhabdomyoma usually present an extremely varied picture. The fibers, if any are present, are not arranged in parallel rows and connected in large bundles, as in the case of leiomyoma, but appear more often singly and intertwining in every possible plane. In rare cases fairly well-developed muscle-fibers with distinct transverse striation, visible throughout the entire thickness of the fiber, are found; while, on the other hand, narrow ribon-shaped or wavy elements with incomplete striation are quite frequent. The sarcolemma is almost always absent, or it may be recognizable here and there as a delicate membrane near the nucleus. The cells most frequently seen are cylindric (or tubular) in type, and present an outer, transversely striated envelop, containing in its interior a granular sarcoplasm with one or more nuclei. The nuclei may be arranged one behind the other in closely packed rows, producing tubes solely made up of nuclei; or, if the nuclei are larger and less numerous, the wall of the tube presents a bulging at intervals corresponding to the position of the nuclei, thus constricting the wall at various points and producing spindle-shaped figures. The transversely striated outer zone may be extraordinarily thin, and, in fact, may not be demonstrable at all; in such cases the cellular structures are spindle-shaped and suggest smooth muscle-fibers, with which they have unquestionably often been confounded. The longitudinal striation of the fibers and spindles is often well developed, and at the end of the cells a fraying-out of the fibrils contained within the cells is sometimes observed from the loss of the cement-substance, which normally holds them together. In microscopic sections these fibers are seen in various planes or appear as circular, loosely granulated structures, devoid of nuclei, or, containing several nuclei together at their centers. In addition to the cells that appear in the form of fibers even more widely aberrant structures, such as club-shaped, pear-shaped, oval, and circular cells, are observed, which sometimes exhibit in their peripheral portions a suggestion of transverse striation in the form of radiating or concentric markings and frequently contain several nuclei in their interior. It has been repeatedly pointed out that the granular sarcoplasm often contains glycogen granules in large numbers. *Rhabdomyoma of the heart* usually exhibits a peculiar structure; it consists of large, branching, spider-like cells, which are hollow at the center, or sometimes contain nuclei in their hollow interior, so as to present the appearance of meshes in cross-sections. Seiffert attributes this peculiar structure to the development of greatly enlarged embryonal muscle-cells.

From the presence of cells with imperfectly developed transverse striation and of cells in which the transverse striation cannot be demonstrated at all it has been concluded that the elements of a rhabdomyoma may develop from smooth muscle-cells; in other words, it has been assumed that a direct conversion of smooth fibers into transversely striated fibers takes place. It has already been seen that, as a matter of fact, any transitional stage between non-striated and striated cells may be observed in the same tumor; but this is far from indicating that these unstriped muscle-cells are identical with the genuine smooth muscle-cells of the involuntary muscles of the body. The occurrence of such a conversion is unlikely on developmental grounds, and we would do great violence to the doctrine of the specificity of cells in accepting such a hypothesis.

The origin of rhabdomyoma (or rhabdomyosarcoma) may be attributed in part to the displacement of muscle-germs during fetal life (from the myotomes of the primary vertebræ) and partly to actual neoplastic proliferation of preëxisting striated muscles. The first group would include chiefly the rhabdomyomata of the kidney, which probably furnish the largest contingent in this rather uncommon class of tumors, rhabdomyoma of the pelvis of the kidney, the urinary bladder, the uterus, the testicle, and the vagina. The second group would include the rhabdomyomata of the heart, the esophagus, and the skeletal muscles. Even in the latter the assumption of a congenital origin—from germinal material that has been left behind and that has not been utilized—cannot be altogether discarded, as the tumor-elements usually exhibit a great morphologic similarity with normal striated muscle-fibers at certain periods of their development (primitive tubes).

Neuroma.

A genuine neuroma consists exclusively of newly formed nerve-fibers and cells. Accordingly we distinguish (Virchow) the fibrillar and the cellular or ganglionic neuroma, and as the nerve-fibers may be medullated or non-medullated, we also distinguish myelinic and amyelinic neuroma.

True neuroma is exceedingly rare, although certain changes in preëxisting nerves of an entirely different nature are erroneously included among them. In the description of fibroma it was pointed out that a tumor consisting solely of connective tissue quite frequently takes its origin in nerves, developing either from the endoneurium or from the perineurium. Such tumors cause a spindle-shaped enlargement in the affected trunks and are distinguished by their multiple appearance and frequently symmetric character. They are quite commonly described as "*neurofibroma*," although the nerve tissue in them remains entirely passive and quite frequently is even injured by the fibrous growths. These connective-tissue tumors may even grow from nerves that have been divided and are already in a stage of degeneration. It is evident, therefore, that there can be no question in these cases of a new formation of nerve-fibers, and it is accordingly unjustifiable to speak of a neurofibroma when the condition is merely a simple fibroma of nerves, the connective-tissue envelop furnishing the matrix for the tumor.

The conditions are similar in the case of so-called *plexiform neuroma* ("Rankenneurom," v. Bruns), a hyperplastic formation occurring chiefly in the nerves of the face, the neck, and the chest, and leading to the production of masses of interlacing and tortuous strands of tissue presenting irregular enlargements. When these tumors are examined under the microscope, it is found that they contain connective tissue in greater preponderance—that is to say, they are the result chiefly of the proliferation of the endoneurium and perineurium, forcing the preëxisting nerve-fibers apart, and surrounding them with thick masses of fibers. It is needless to say that the nerve-fibers unquestionably experience an increase in length, especially when the bundles of fibrous tissue exhibit great tortuosity, and in that sense it is not to be denied that the nerve-tissue takes some part in the formation of these tumors. Its share in their production, however, is not of a kind to justify our speaking of them as true "neuromata."

The so-called "*traumatic neuroma*," *amputation neuroma*, or *stump neuroma*, has a stronger claim to be included among true nerve tumors. These terms are applied to the knob-like, usually much indurated enlargements, which frequently develop after a time at the divided ends of nerves in amputation-stumps (Plate 48, Fig. 2). They also consist of abundant masses of hard, fibrous tissue derived from the connective tissue of the nerves; but when a longitudinal section from the lower end of the nerve, including the nodular outgrowth, is examined, it is found that new fibers have grown from the divided end of the nerve, and after undergoing dichotomous division, have grown out in all directions, completely surrounding the original nerve-stump and thus becoming chiefly responsible for the enlargement that results. Sometimes there are found among the nerve-fibers transitional forms between nucleated and medullated fibers, so that, when Weigert's medullary-sheath stain is used, it is not always possible to bring the fibers uniformly into view; surrounding the nucleated fibers an envelop covered with nuclei is found, which probably corresponds to the sheath of Schwann. Part of the axis-cylinder probably remains permanently devoid of a medullary sheath. We, therefore, have to do here with a new formation of nerve-fibers that have their origin in old fibers; but it is a question, nevertheless, whether this means that the process represents a genuine tumor formation. It would appear rather to represent a kind of regenerative process which remains incomplete because there is no peripheral nerve-end with which the proximal end may unite, as in the case of division of the nerve or excision of a large section (compare p. 156).

It follows, therefore, that the domain of the true neuroma is very much restricted. Judging from the small number of observations that have been published, they seem to be entirely confined to the sympathetic nervous system, where they appear as nodular, soft, slightly transparent tumors. They usually contain large quantities of ganglion-cells, in part pigmented and often characterized by the presence of many nuclei. Sometimes it is possible to trace a nucleated envelop from the nerve-fibers, which are provided with a sheath of Schwann, to the ganglion-cells; here and there the latter even appear to be surrounded by a mantle of myelin as a continuation of the medullary sheath (M. B. Schmid, Borst).

These tumors have been found most frequently in the neighborhood of the thoracic and abdominal vertebral column, more rarely in the skin. They probably take their origin in nearly every instance from preëxisting ganglia of the sympathetic nerves.

Glioma.

The term glioma or neuroglioma is used to designate a form of tumor occurring exclusively [principally.—Ed.] in the central nervous system, which results from the proliferation of a specific supporting substance known as neuroglia. This tissue, like the nerve-cells, is derived from the epithelium of the medullary tube—*i.e.*, from derivatives of the ectoderm. It would, however, be in-correct, on this account, to compare these tumors with epithelial structures, because the neuroglia only represents a supporting substance that has been differentiated in a definite way; in other words, the stroma of the central nervous system. Glioma is, therefore, more properly classified with connective-tissue new formations having their origin in mesenchymatous derivatives. Their polymorphous character and the great morphologic similarity to the last-mentioned tumors also justify such a view.

The neoplastic character of glioma is often indistinct as compared with that of other new growths. As a rule, the tumors do not represent distinctly circumscribed, nodular deposits in the tissue; on the contrary, they manifest themselves merely by the preponderance, in the region of their distribution, of neuroglia over nerve-cells and fibers, although the latter may, it is true, disappear altogether. The boundaries of this neurogliar proliferation are accordingly ill defined, as the tissues gradually merge with the surrounding nerve-substance, which becomes infiltrated by the advancing tumor. For this reason a glioma even macroscopically does not appear as a well-defined projection into the brain-substance, nor in the form of scattered nodules in the tissue; but betrays itself rather by diffuse, indistinctly limited increase of consistence, the color varying from a translucent grayish white to grayish red, depending on the quantity of blood that is present. A glioma may reveal itself only by a barely perceptible enlargement of certain portions of the central nervous system, and the tumor in its growth never oversteps the physiologic boundaries of the organ; thus, for example, it never infiltrates or perforates the meninges.

The slow growth and gradual advance, with infiltration, of these tumors sufficiently explain why the clinical phenomena to which they give rise during life are so slight. Distinct symptoms are produced in many cases only when the intracranial pressure is greatly increased or when primary apoplexy is simulated by the occurrence of a secondary hemorrhage.

The typical glioma is seen in tumors composed of many

PLATE 48.

FIG. 1.—**Cells from a So-called Glioma of the Retina Freshly Isolated** (× 675).

FIG. 2.—**Glioma of the Cerebrum** (Hemat.-eosin. × 625): 1, Small round-cells with distinct processes; 2, larger round-cells without recognizable processes; 3, connective-tissue cells: 4, processes of glia-cells.

FIG. 3.—**Amputation Neuroma** (**So-called Stump-Neuroma**) **From the Sciatic Nerve** (Weigert's Medullary Sheath Stain. × 80): 1, Medullary nerve-fibers in longitudinal section; 2, transverse sections of such fibers; 3, connective tissue.

FIGURE XIV.

Glioma Sarcomatosum of the Right Cerebral Hemisphere (× 280): 1, Glia-cells with distinct processes; 2, multinuclear cells, the processes of which unite with those of the uninuclear glia-cells; 3, blood-vessels.

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small cells containing a very small proportion of protoplasm and a round, dark, granular nucleus, filling almost the entire cell-body and sending out delicate radiating fibrils which interlace to form a felt-like ground-substance. According as the cells are more abundant and more densely packed or the fibrillar ground-substance preponderates, various degrees of consistence are produced, and we accordingly distinguish soft and hard gliomata. The fibers correspond to the supporting fibers of the neuroglia, which normally take the place of connective-tissue stroma in the central nervous system; it has never been absolutely proved whether they really have their origin in the cell-bodies or merely are in close apposition with them (Weigert). At any rate, they vary greatly both in length and in thickness. Sometimes we find true cells surrounded by a radiating wreath of fibers (*spider-cells*, *astrocytes*); or cells with very long, wavy, and delicate fibers ("Langstrahler"); or cells with their heavy processes attached to the cell-body by a broad base ("Kurzstrahler"). Sometimes there seems to be a definite relation between the fibers and the blood-vessels, the former being apparently

Tab.48.

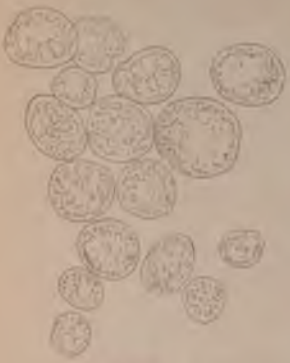


Fig.1.

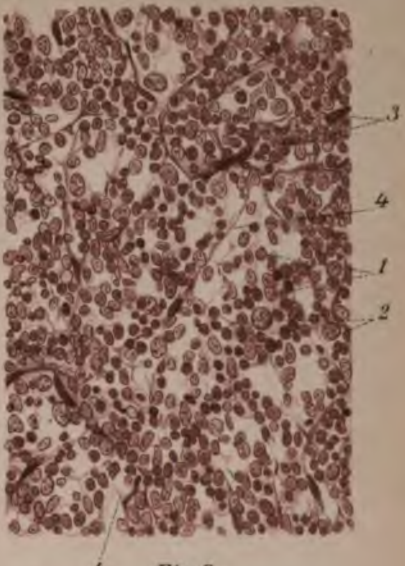
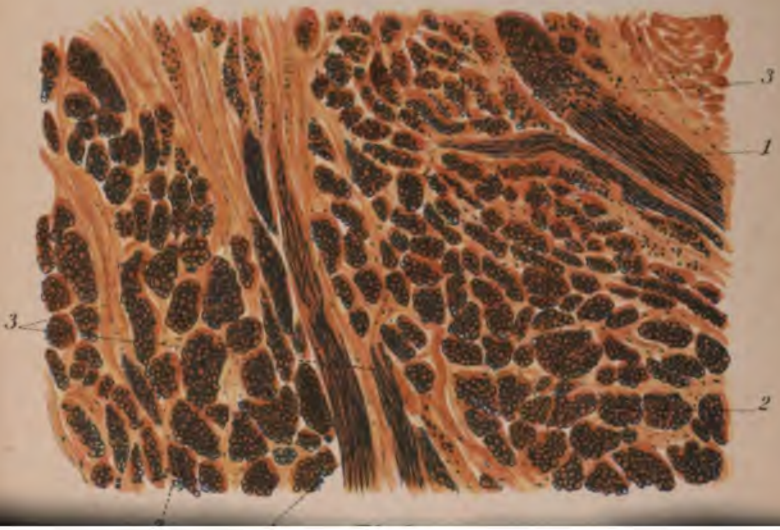


Fig.2.



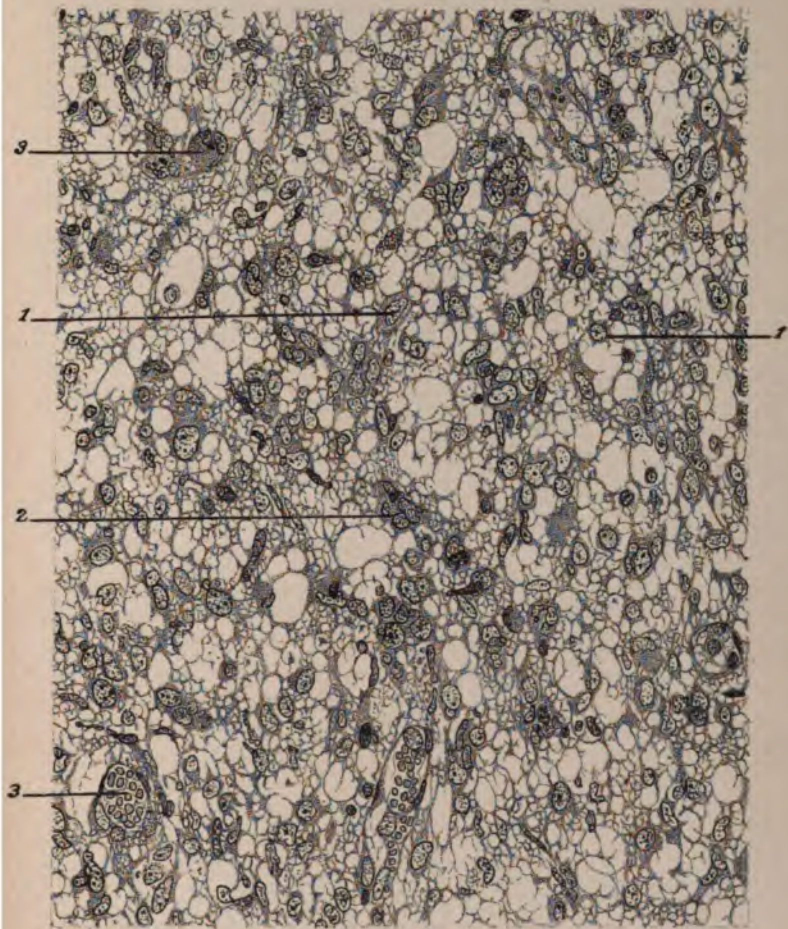


Fig. XIV.

adherent to the vessel-walls. Anastomosis of the fibers among themselves does not appear to occur. The irregular network of fibers thus produced forms the ground-substance of the tumor-tissue; there is no other, either homogeneous or granulated, matrix, although, from the fact that in microscopic sections many of the smaller fibrils are cut transversely, a finely granular interstitial tissue may be simulated. As in the normal central nervous system, so in the tumors derived from its tissues, the neuroglia is extremely perishable and prone to cadaveric changes; hence, owing to postmortem disintegration or to improper fixation and staining, the fibers often do not appear as distinctly as might be desirable; they may even fuse to form a homogeneous or finely granular mass.

Numerous deviations from this type of glioma are observed, particularly as regards the shape and size of the cells and the arrangement of the fibers. The cells may present every transitional form from the small round elements, almost devoid of protoplasm, to very large polygonal cells, rich in protoplasm, and bearing an extraordinary resemblance to ganglion-cells or even to giant-cells possessing a great number of nuclei. The likeness to ganglion-cells is often striking, which is not surprising in view of the genetic connection between the glia-cells and nerve-cells and their common origin from the ectodermal matrix of the medullary tube.

(According to Ziegler, an actual new formation of ganglion-cells takes place in many forms of glioma, for which he proposes the term *neuroglioma ganglionare.* Such of these tumors as contain nerve-fibers as well might perhaps be included among neuroma.)

Needless to say, corresponding differences are also observed in the nuclei. As the cells enlarge, the nuclei also become larger, paler, and more vesicular; in addition to the small dark cells, consisting almost exclusively of nucleus, spindle-shaped elements with elongated nuclei are observed, and the fibers grow out from the poles of the cells either singly or in the form of a brush (Plate 48, Fig. 2). In addition, there are found a few multinuclear cells or even true giant-cells, in which it is even more difficult, if not quite impossible, to demonstrate any connection with the fibers. With the increasing multiformity of the cells the recognition of these tumors becomes more and more difficult, especially when it is found impossible to demonstrate any connection with neuroglia-fibers. The tumor is likely to be mistaken for a sarcoma. It is not, as a rule, permissible, however, in these cases to speak of a "gliosarcoma," since the condition is not a combination of glioma with a sarcoma. The term "*glioma sarcomatodes*" would appear to be more justifiable. What decides the diagnosis in every case is the finding of fibers and the proof that they are neurogliar, and not connective-tissue, fibers. But in the case of sarcomatous tumors that encroach upon the central nervous system it is necessary to guard against confusion with possible remains of pre-existing neurogliar tissue.

A special formation, which lends a special stamp to many gliomata and is of importance in a histogenetic sense, consists of epithelial inclusions that are sometimes found. These are circular, cystic cavities or clefts, lined on their inner surface with cylindric epithelium, and thus suggesting at the first glance the remains of ependyma. As a matter of fact, they may be explained by the assumption that buds have been cut off from the normal cavities of the central nervous system which are lined with ependyma; on the other hand, however, their origin may also be attributed to a kind of retrogressive metamorphosis of glia-cells into ependyma cells, especially as it has sometimes been found possible to demonstrate in the extremities of the epithelial cells, away from the lumen, basal fibrillar processes bent at various angles and connected with the remaining fibrillar network.

These cavities, lined with epithelium, are quite common in the spinal cord, where, neurogliar neoplasms usually assume a long, cylindric shape. Sometimes a connection with the ependyma of the central canal is demonstrable ("*central glioma*"). In other cases such a connection is not made out.

Sometimes large cavities are thus produced in the spinal cord in cases of glioma, and as such cavities, when the epithelial lining can be demonstrated, are generally described as "*syringomyelia*," a large proportion of the cases of syringomyelia should be regarded as primary glioma. Of course, these "gliomata" of the spinal cord are not to be confounded with the increase of glia-tissue, so-called "glioses," due to a reactive proliferation in response to some inflammatory irritant (see Spinal Cord, *Atlas of Special Pathologic Histology*, Vol. II.). [Mallory has described a glioma developing in the sacral region, presumably from remains of the neural canal.—Ed.]

Gliomata not infrequently become the scene of retrogressive metamorphosis. Owing to defective vascularization or embolic processes, softening takes place and runs a course similar to other processes of the same kind in the central nervous system. There is no coagulation of albumin (coagulation-necrosis), as in other organs; on the contrary, a process of liquefaction takes place. In addition to the necrotic masses of detritus large quantities of the well-known so-called "softening-cells" make their appearance—*i.e.*, contractile cells with large circular bodies, which become loaded with fat-droplets and minute tissue-detritus, and in a recent, teased preparation appear as "granule cells" or "granule spheres." They may accumulate in such masses as completely to obscure the tumor-tissue and render it unrecognizable. The gradual absorption of the softened portions leads to the formation of cavities filled at first with a milky and later with a watery fluid—cysts in every respect similar to those due to similar causes in the brain-substance. When the softening process erodes the walls of blood-vessels, which are sometimes quite numerous in glioma, or a vessel ruptures from the external pressure, extensive hemorrhages with more or less wide-spread destruction of tissue occur, and this accident is often the immediate cause of the first clinical manifestation of a tumor, which in such cases usually leads to a diagnosis of apoplexy. Even at the postmortem table the diagnosis may present considerable difficulties, the hemorrhage being by far the most imposing manifestation, and making it difficult to find the tumor.

Metastasis has practically never been observed to take place in glioma of the central nervous system. [In Mallory's sacral glioma metastases developed.—Ed.]

An entirely different character from that of glioma of the central nervous system is observed in so-called *glioma of the retina*, which is supposed to take its origin in the nuclear layer of the retina. Clinically and macroscopically it is distinguished by more rapid growth, extreme malignancy, a marked tendency to metastasis, and great destructiveness to neighboring tissues. On microscopic examination the tumor is found to consist of a dense mass of small round-cells, which usually do not possess any fibrous processes, and in a recent teased preparation appear as isolated spheres of varying sizes with imperfectly outlined nuclei. It is probable that in most cases [especially of those with metastases.—Ed.] the tumor is not a true glioma, but rather a small round-cell sarcoma. When delicate fibrous processes are present, it is true that the similarity to glioma is striking. In these tumors cavities lined with rod-shaped epithelial cells are sometimes present, or the round-cells may be arranged about these cavities in the form of a roset, a formation that has suggested the term "neuro-epithelioma" (Wintersteiner [Brown Pusey]). [Other authors emphasize the gliomatous nature of these particular retinal tumors.—Ed.]

Angioma.

The term angioma is applied to a tumor consisting in the main of newly formed vessels. A *hemangioma* is a tumor composed of blood-vessels; a *lymphangioma*, one consisting of lymph-vessels. Strictly speaking, the term hemangioma should be restricted to tumors in which the new formation of blood-vessels actually can be demonstrated; it should not be applied to any kind of swelling that owes its origin to special distention of preëxisting blood-vessels or to hypertrophy of their walls. It will be seen presently that the distinction between new formation and dilatation presents great practical difficulties in the case of blood- and lymph-vessels, and that certain transitional forms are unavoidably included in the category of genuine tumors. It is almost needless to say that all enlargements due to the dilatation of large vascular channels or trunks—in other words, aneurysms and varices, as well as so-called plexiform or racemose arterial angiomata ("Rankenangiom")—must be strictly excluded, as such conditions present merely an extreme development or exaggeration of normally existing vascular channels and do not belong to the domain of tumors, even when it is possible to demonstrate the abnormal development of tissue in the walls of the affected vessels, for the latter is only a secondary phenomenon due to an abnormal increase in the lumen and changes in the circulatory conditions.

It will be shown also that there is a group of angiomata, including examples both of hemangioma and of lymphangioma, which present certain points of contact with another form of tumor that begins primarily in the proliferation of a certain kind of cell in the vessel-walls, namely, *endothelioma.* As a matter of fact, a good deal of confusion has arisen on this subject, owing to arbitrary nomenclature and its indiscriminate application, as will be shown more at length in connection with certain forms of sarcoma and endothelioma. In a general way, it may be said, in order to differentiate between morphologically related forms of tumors, that the term angioma should not be used unless it is possible to demonstrate that the newly formed canals are in communication with the rest of the vascular or lymphatic systems of the body, and that the contents of these canals are the same as that of the general vascular or lymphatic system.

Hemangiomata are divided into three main forms, in accordance with their development and structure:

1. Hæmangioma telangiectaticum.
2. Hæmangioma cavernosum.
3. Hæmangioma hypertrophicum.

PLATE 49.

FIG. 1.—**Hæmangioma Fibromatosum from the Neck** (Hemat.-eosin. × 160.): 1, Broad connective-tissue interstices; 2, vascular spaces; 3, vascular spaces seen in transverse section, lined with tall elements resembling epithelium.

FIG. 2.—**Nævus Vasculosus from the Skin of the Abdomen** (Hemat.-eosin. × 150.): 1, Epidermal covering; 2, cuticle with flattened papillary body; 3, capillaries filled with red blood-corpuscles and cavities bounded by distinct endothelium.

The first of these forms, the telangiectatic angioma (also known as *hæmangioma simplex*), is usually a flat, superficial tumor, found most frequently in the skin, both in the corium and in the subcutaneous tissue, and for the most part consisting of capillary blood-vessels (*nævus vasculosus*). It either occupies the position of the normal skin, in which it forms circumscribed, bright-red (*nævus flammeus*, "fire-mark"), or dark bluish-red (*nævus vinosus*) spots; or it causes a wart-like projection of the cutaneous tissue and then represents a true mulberry-like tumor (*nævus morus*), in which the quantity of blood varies greatly under different conditions ("erectile tumors").

On histologic examination the blood-vessels appear as thin-walled tubes, usually with but one layer of endothelium. The lumen varies as to width with the degree of distention. On the outside these endothelial tubes, which are often irregularly tortuous or corkscrew-shaped, are in immediate contact with fibrous connective tissue, which usually is quite rich in cells; the layers opposed to the vascular tubes, as a rule, contain a greater number of cells, which are also of a more embryonal type (Plate 49, Fig. 2).

From this peculiarity it has been concluded (v. Rindfleisch) that the primary change in this formation is a proliferation of fibrocellular tissue and not an increase of blood-vessels, the blood-vessels being dilated and elongated secondarily by the traction on their walls of the fibrous tissue. It is a fact that these telangiectatic angiomata, especially when they extend into the subcutaneous adipose

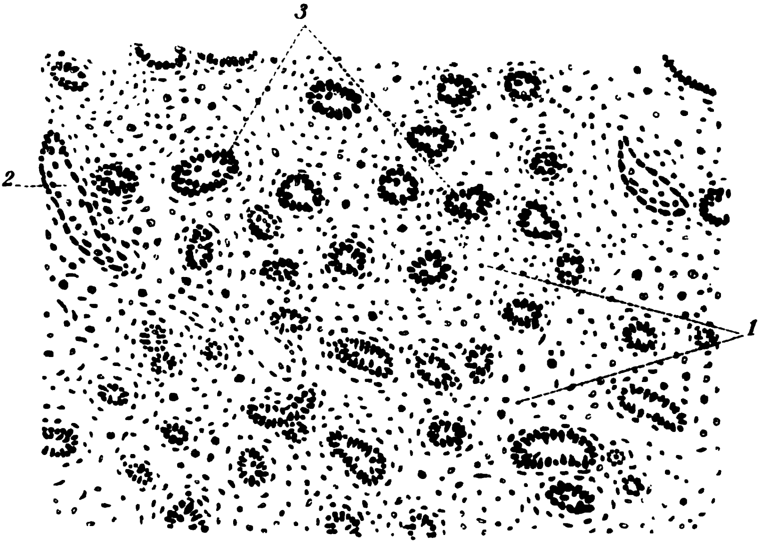
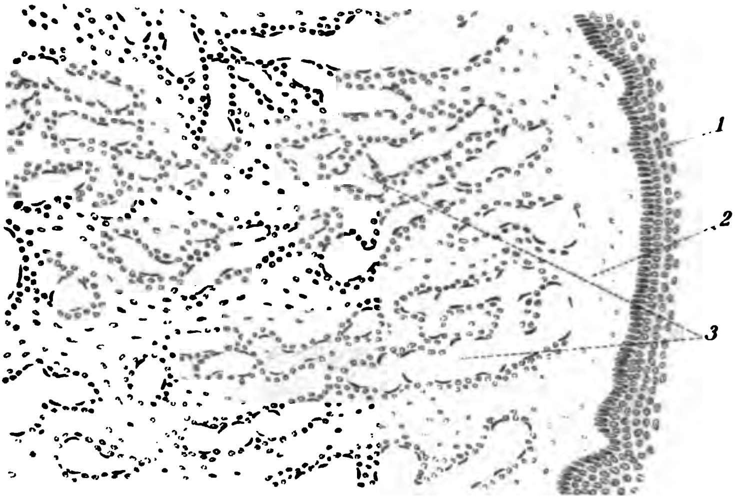


Fig. 1.



tissue, often exhibit a typical lobular structure, in every respect similar to the arrangement of the fat-lobules, and in the marginal portions embryonal fibrous tissue rich in cells develops between the fat-cells near the capillaries, becoming more and more distinct as it approaches the corium. Strictly speaking, these tumors ought, therefore, since they are originally derived from fibrous connective tissue, be designated *telangiectatic fibromata*, and, in fact, it is often exceedingly difficult, if not impossible, to distinguish between vascular fibromata and this variety of angiomata. The papillary body of the cutis overlying the telangiectatic areas is usually obliterated, which gives the skin a naked-eye appearance of smoothness, tenuity, and translucency.

Other organs, as the brain, bones, glands, mammary gland, may also be the seat of telangiectatic tumors. If the tissue lying between the blood-vessels becomes cellular and contains numerous embryonal immature forms, the term *angiosarcoma* is used (Plate 55, Fig. 1).

The second form of angioma, *cavernous angioma* or *cavernoma*, so far as its structure is concerned, suggests the cavernous body in the external genitalia. In this tumor vascular tubes cease to be regular; the cavities filled with blood appear as irregular, circular or sinuous spaces, in transverse section polygonal, or presenting ridge-like projections, resulting in a structure that suggests a sponge more than anything else. On the inner side the walls of the cavities are usually lined with a low endothelium, which, however, cannot usually be traced in a continuous line, and in cross-sections is often difficult to distinguish from the surrounding connective tissue; in many places it seems to be actually wanting. For the rest, the septa between the lacunæ are formed usually of mature fibrous tissue with an admixture of elastic fibers in varying numbers and occasional smooth muscle-fibers.

The commonest seats of cavernoma are the skin and the liver. In the skin transitional forms between angioma simplex or telangiectasis and cavernoma are often observed. As in the case of a simple angioma, the origin

PLATE 50.

FIG. 1.—**Angiocavernoma of the Liver** (Hemat.-eosin. × 70.): 1, Liver-tissue; 2, cavernous spaces filled with blood; 3, connective-tissue capsule separating them from the liver-tissue.

FIG. 2.—**Lymphangioma of the Neck** (Hemat.-eosin. × 250,): 1, Transverse sections of lymph-vessels with tall endothelium; 2, masses of endothelial cells in transverse section; 3, connective-tissue framework.

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of cavernoma may be attributed to the development of connective tissue in the wall of preëxisting blood-vessels and secondary distortion of the vessels.

Cavernoma has also been attributed to irregular dilatation of smaller veins, with connective-tissue changes of their walls and partial confluence of the lumens.

The classical form of cavernous angioma is found in the liver, where it is often multiple. Its size is variable. Solitary forms have been observed, ranging from a pinhead to a tumor, that caused an enlargement of the organ equal in size to the uterus in the last months of pregnancy. The origin of the tumor is variously explained. The fact that the hepatic cavernoma is most frequent in advanced age and is sometimes multiple and associated with passive congestion would seem to favor the view that it grows from preëxisting hepatic blood-vessels, a view which is further supported by the fact that the connective-tissue septa sometimes harbor isolated cords of atrophic liver-cells or individual liver-cells, as well as by the fact that transition from conditions due to persistent, extreme passive congestion (Plate 8, Fig. 1) to true cavernoma formations are observed. The fact that the capillary walls, which break down after the cells have disappeared, undergo a connective-tissue increase finds its analogue in the processes which we have observed elsewhere in chronic congestive conditions.

On the other hand, the observation that hepatic cavernoma sometimes occurs in suckling infants and young children, is often solitary, and in that case usually separated from the surrounding liver-tissue by a connective-

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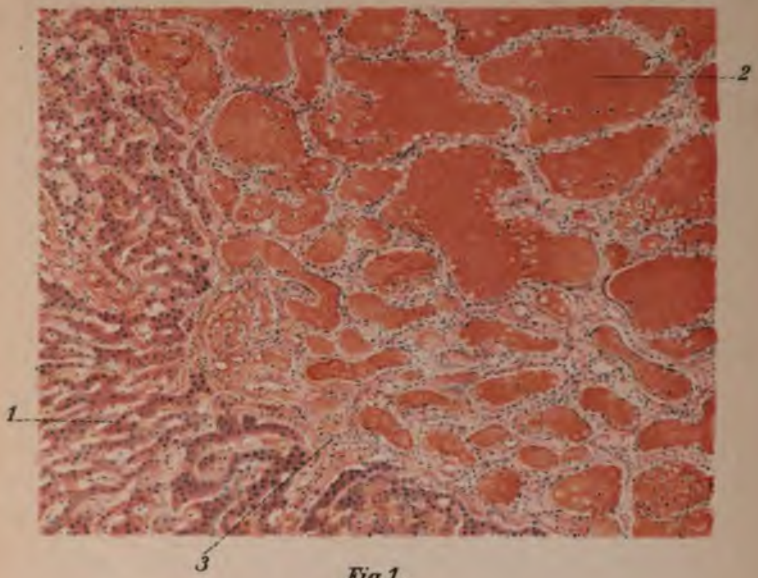
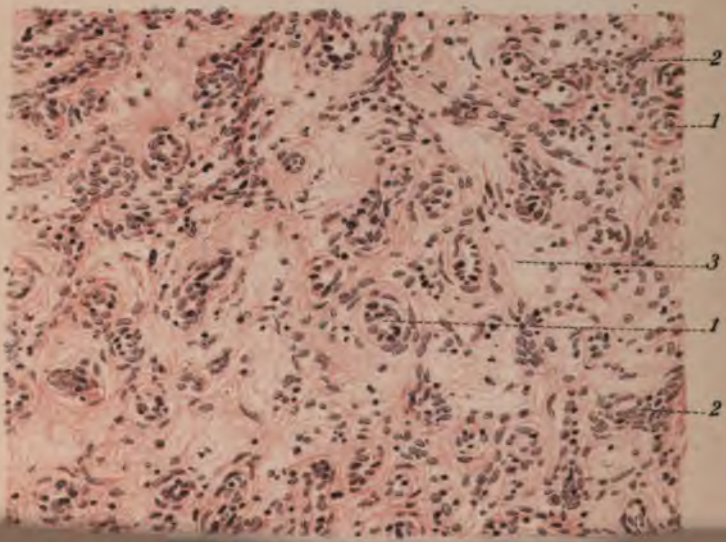


Fig.1.



tissue capsule, argues altogether against its origin from preëxisting (functionating) hepatic vessels. Ribbert accordingly attributes its origin to some histogenetic disturbance in the development of the liver-tissue.

Cavernoma has also been observed outside of the liver, in the brain, bones, spleen, intestine, bladder, uterus, and muscles.

A few words should be devoted to a discussion of the *hypertrophic angioma*, a form which was first separated from other tumors of the same class by Ziegler. It is distinguished from the two forms which have just been described by the fact that the new formation of blood-vessels is accompanied by definite proliferation of other cells. It may occur in the form of *hæmangioma simplex* or of cavernoma, but most frequently the former. The first glance at the microscopic picture suggests a glandular, rather than a vascular tumor, and the true nature of the neoplasm is recognized only by the transitional forms and by partial filling of the cavities with blood. The lumens are lined with large cylindric cells, with an abundance of protoplasm, and often cuboidal in shape, instead of with endothelium, so that transverse sections present the greatest similarity to those of glands or the gland-ducts. This similarity is especially marked in bloodless and contracted portions of the tissue. When the contraction is extreme, several layers of these cells, superimposed one upon the other, are recognizable, and as the channels become more and more filled with blood, the cells also appear more flattened and the endothelial character becomes more distinct. This hypertrophic development of endothelium in the cavities has also been observed in cases of cavernous angioma (Ziegler, Schadeldach). It should be pointed out, however, that in many organs—for example, in the ovary and uterus—the endothelium of the blood-vessels is normally quite tall.

Lymphangioma.—So far as its histologic structure and its origin are concerned, lymphangioma presents the greatest similarity to hemangioma. In the first place, the same difficulty exists in distinguishing true tumor-formation of lymph-vessels (which, strictly speaking, should be a *sine quâ non* in the definition of a lymphangioma) from dilatation of preëxisting lymph-vessels and proliferating processes in them. In the broader sense, that is to say, if we include any tumor-like hyperplasia of the lymphatic apparatus, the domain of the lymphangioma is a very large one. It is, however, seldom possible to demonstrate a true formation of lymph-channels that shall be beyond the reach of criticism.

Lymphangioma develops most frequently in the skin and in mucous membranes; or, rather, it is either subcutaneous or submucous. A division entirely analogous to that of hemangioma results in three main forms: 1. *Lymphangioma simplex* or lymphangiectasis. 2. *Lymphangioma hypertrophicum.* 3. *Lymphangioma cavernosum.* To these forms it is common to add a fourth, *lymphangioma cysticum.* Simple lymphangiectatic tumors consist usually of a convolution of lymph-vessels imbedded in the fibrous and more or less cellular connective tissue. The lymph-channels consist of endothelial tubes which frequently contain, in addition to fluid lymph, a large number of lymphocytes; here and there thrombi may form which in turn may, of course, become organized by the ingrowth of surrounding tissue. Sometimes it is actually possible to demonstrate the proliferation of lymph-vessels; bud-like endothelial plugs are seen growing into the adjacent connective tissue from the walls of the tubes. As in the new formation of blood-vessels, these cellular threads are at first solid and later develop a lumen or canal by the separation of the cells at their base. In the connective tissue it is also possible to demonstrate various proliferative conditions. It is often found to contain collections of lymphocytes, resembling follicles, in the neighborhood of the lymph-vessels, so that the structure frequently assumes an adenoid character. Sometimes it is edematous and swollen, and the fibers are quite loosely arranged.

The *hypertrophic form* in a sense represents a variety of this simple lymphangiectasis. In this tumor, as in the hypertrophic hemangioma, the endothelial cells have become converted into large cuboidal or cylindric cellular structures with an abundance of protoplasm, which either form a continuous lining on the inner surface of the tube or project into the lumen-like villi, thus producing structures resembling gland-ducts (Plate 50, Fig. 2).

Lymphangioma of this type is found most frequently as a congenital structure imbedded in the skin. Sometimes it causes a bulging in the form of a wart, or it gives rise to merely a flat or slightly elevated protuberance. When individual vascular regions are distended more than others as the result possibly of congestion they may became cystic and rise above the level of the skin, finally breaking through and leading to the formation of weeping papules (*lymphorrhea*). Many congenital nevi on close examination are found to consist of such superfluous or proliferated lymph-vessels. Sometimes they are darker in color, owing to the presence of a dark or yellowish pigment. The flat, so-called liver spots and freckles (lentigines) also belong to this category. When the lymph-vessels which chiefly make up the tumor lose the character of tubular and canalicular structures and take the form of irregular, ampullar, spindle-shaped and polygonal cavities, the term *cavernous angioma* is employed. The connective-tissue septa which join the endothelial lining usually contain, in addition to lymphocytes, elastic fibers and muscular elements. Many congenital enlargements, especially about the head and the external genitalia, owe their origin to a diffuse collection of cavernous lymphangiectatic tissue of this kind. Thus, for example, the disfiguring congenital enlargements of the tongue, lips, and cheeks, known respectively as macroglossia, macromelia, and macrocheilia; congenital enlargement of the labia and of the scrotum, and many congenital cavernous tumors of the mesentery. The latter are designated *chylangioma* on account of the milky material which they usually contain and their connection with the lacteals.

Finally, the cavities formed by lymph-vessels may undergo cystic distention and thus lead to the formation of multilocular cystic tumors of complicated structure. Their origin is probably attributable to an increase in the internal pressure from stasis, which often begins in fetal life. The tumors are most frequently found on the neck, where they form extensive growths, designated *hygroma colli cysticum congenitum.* The endothelium in these cysts is low, often atrophic, owing to the great pressure; or it is loosened and cast off as the result of maceration. The connective tissue presents the evidences of swelling and contains cleft-like cavities filled with edematous fluid.[1]

Many forms of *elephantiasis* may be included among the acquired cystic lymphangiomata; in this condition the lymph-clefts often undergo enormous cystic dilatation, usually as the result of thrombotic obstruction of the channels occurring in chronic inflammatory processes (relapsing erysipelas). True new formation of lymph-vessels can, however, hardly be said to occur in this disease.

SARCOMA.[2]

Since Virchow published his definition, the term sarcoma has been applied to a tumor composed of cellular elements belonging to the connective-tissue group. As the neoplasm is formed solely from this one kind of tissue, it is included among the histoid tumors, as has already been stated. It will be seen later that this designation is justifiable only with certain reservations.

The characteristic feature of sarcoma is the enormous preponderance of the cellular constituents over the ground-substance, a condition exactly the reverse of what is observed in mature connective tissue. The tumor, therefore, imitates not the mature, but the embryonal immature type of connective tissue and remains stationary at a stage which is only a temporary condition in the development of normal connective tissue. The cellular progenitors of connective tissue do not attain their full physiologic growth, and fail to produce long-drawn-out fibers arranged in parallel rows or interlacing network; in other words, the tissue never matures, its development being arrested at an early stage and the cell-production being, as it were, precipitate. As this cell-production is practically unlimited and never ceases, the original connective-tissue character often disappears altogether at the height of tumor development, and one is only vaguely reminded of it by certain properties of the cellular elements. It is a remarkable fact this "youthful stage" of connective-tissue substance, which in a sense becomes stationary in the development of sarcoma, may correspond both to a certain stage in the true embryonal genesis of connective tissue—such as is observed in the differentiation of the mesenchyma and the invasion of the germs of that tissue in the formation of supporting substance in all the organs—and to a developmental cellular stage of connective tissue which takes place in the so-called "inflammatory neoplasms." The extreme variability of the cellular components in the processes which have been described in the chapters on Inflammation and Regeneration, and the fact that every stage in the development of the cellular portion of connective tissue may appear in a sarcoma as part of the tumor and become fixed, as it were, explain the extraordinary abundance of forms and the great morphologic variety of the elementary constituents of these tumors. Every form and variety in the long scale of development, from the small round-cell with very little protoplasm to the multinuclear giant-cell, from the spindle-shaped fibroblast to the extensive, polygonal plasma-cell, may be represented in the sarcoma—*i. e.*, the tumor consists either exclusively or chiefly of one of these cell-varieties, or a large number of different varieties of the forms take part in the formation of the tumor.

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[1] Certain sacral tumors consist entirely of a conglomeration of lymphatic cysts.

[2] Sarcoma (σάρξ, flesh) is called a fleshy tumor on account of its resemblance to flesh—*i. e.*, luxuriant granulations.

The development of the ground-substance in a sarcoma is equally variegated and polymorphous. We may meet with any one of the derivatives of the mesenchyma that is known to exist; these derivatives may vary greatly in [illegible] as compared with the cells; and finally they may occur in all imaginable mixtures and reciprocal relations. Sometimes the intercellular substance of the sarcoma is difficult to demonstrate, although one of the most important requirements in the diagnosis of "sarcoma" is the possibility of demonstrating such an intercellular substance. The shape of the cell, as has just been pointed out and as will be shown more particularly later on, fails to afford any trustworthy or even useful information, since, as has been mentioned, it is extremely variable. It has been already pointed out in the general discussion of tumors that there is no essential difference, so far as the individual cell is concerned, between carcinoma and sarcoma—in other words, between the "sarcoma cell" and the "carcinoma cell." It is the histogenesis, the development from the parent soil, that determines what the ultimate nature of the tumor is to be,—whether a sarcoma or a carcinoma,—for the doctrine of the specificity of cells, "*omnis cellula e cellula ejusdem generis*," holds good under all circumstances, even in the case of an atypical tumor, in so far at least as epithelium can give rise only to epithelial tumors and connective tissue can produce only connective-tissue tumors that are always more or less closely related to the arch type. It has already been emphasized that it is usually impossible to determine the histogenesis from morphologic data; it is in the reciprocal relation of cells and their grouping in large cell-complexes that we find the key to the microscopic diagnosis of tumors. We recognize epithelial tissue as such only by the fact that the cells are in immediate contact with one another, without any intervening intercellular substance; the shape of the individual cell being of secondary importance and subject to great variations, not only because the cells influence one another reciprocally, but also on account of metaplastic processes. Connective tissue is characterized morphologically only by the demonstration of the reciprocal connection of the individual cells with a common stratum, the presence of an intervening substance especially adapted to "connect" the cells, with which the cells are in direct communication and which is produced by the cells. This substance we see in its most perfect and most typical form in the mature condition of connective tissue. In tendon, for example, or in a fibroma long fibers are found between the cells, connected with one another as well as with the cells; at the first glance we here recognize a union of the elements to form a common complex. In the embryonal stage of connective tissue, however, the cellular element may predominate to such an extent that its true character is either altogether unrecognizable or recognizable only with difficulty. It is in a sense latent. But the demonstration of a very delicate fibrillar, fibrous, or even granular intercellular substance between the cells is of the greatest importance in determining the nature of the tumor. In certain varieties, especially such as are made up of small, round, cellular elements, it is, in fact, impossible to demonstrate the presence of such an intercellular substance; in these tumors the uniform, diffuse aggregation of a mass of cells of this character, extending over large portions of the tumor, leads the diagnostician on the right track. There is a complete absence of any "alveolar" arrangement of the cells. They are simply scattered among the thin-walled blood-vessels necessary for their nutrition like a mass of indifferent cells in the formative stage, practically representing the type of the earliest embryonal stage of connective tissue. On the other hand, a certain alveolar structure is frequently conspicuous in well-marked examples of sarcoma. "Nest-like" collections of round or polygonal cells, enveloped by denser accumulations of vascular fibrous substance, are found; on closer inspection, however, it is always possible to demonstrate, in the first place, that even within the nest-like cell-complexes there is between individual cells an intercellular substance which is in communication with the protoplasmic processes; and, in the second place, that the intercellular substance is in communication with the fibers of the more robust connective-tissue strands and with the tissue that conveys the blood-vessels (Fig. XVII.).

Finally the intercellular substance and the ground-

FIGURE XV.

Large-celled Sarcoma in Universal Sarcomatosis; Metastases in the Pectoralis Major Muscle (× 385.): Freshly isolated cells with fibrillar processes, in part filled with fat-droplets.

FIGURE XVI.

Sarcoma from the Brain with Well-developed Interstitial Substance (× 300.): 1, Large sarcoma-cells lodged in connective-tissue alveoli; 2, tumor-cells lying singly in small alveoli; 3, well-developed fibrous stroma.

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substance may, like normal connective tissue, present various degrees of higher differentiation. Besides the secretion of fibrils, a formation of other substances of a collagenous nature may take place. Thus, for example, the ground-substance sometimes assumes the nature of true hyaline cartilage in areas of varying extent, and behaves like cartilage even in regard to its chemic constitution; the cells are arranged in more or less closely packed groups in well-developed cartilaginous cavities, while in other portions of the tumor cell-complexes presenting the character of embryonal connective tissue continue to grow (Plate 58, Fig. 1); or foci of osteoid substance (Plate 58, Fig. 2), or of true bone-tissue may form in the intercellular substance. In this way the more highly differentiated combination-forms of sarcoma are produced and we are actually justified in speaking of a "*chondrosarcoma*," an "*osteoid sarcoma*," and an "*osteosarcoma*," in so far as the growth of these different kinds of tissue goes on *pari passu* with that of the embryonal connective tissue.

Cell-proliferation is extremely rapid in most forms of sarcoma, corresponding to the usually rapid and destructive growth of the tumors, and in freshly prepared and suitably preserved sections large numbers of karyokinetic figures are often seen. In addition to the regular forms of mitosis any variety of abnormal segmentation-figures—multipolar, asymmetric mitoses, aberrant chromosomes, *etc.*—may be seen, phenomena which have been described

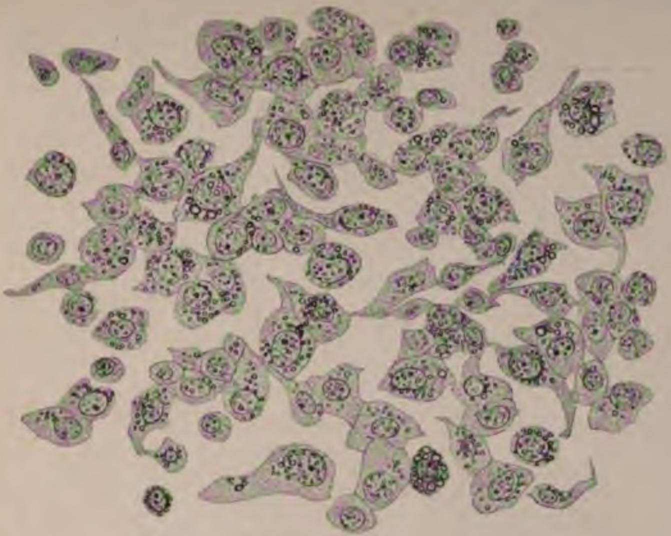
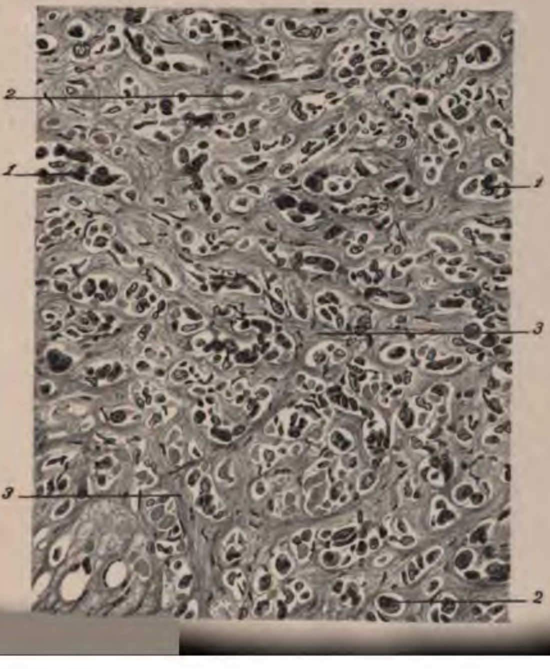


Fig. XV.



in detail in the general discussion of tumors. So-called giant mitoses are found with especial frequency (Plate 59, Fig. 2, and Fig. VIII.), cells in which the chromatin appears to have been broken up into innumerable minute splinters, loops, little spheres, and droplets, the resulting parts being often arranged in the form of a roset.

There can be no doubt that, in addition to indirect mitotic division, direct amitotic division of the nucleus also takes place with special frequency in sarcoma. The result of this process is the formation of bud-like excrescences from the nuclei, which often assume the most peculiar and bizarre forms. In this way the bifurcated, branching, retiform, basket-like chromatin-figures, which are sometimes met in sarcoma, are produced, as well as the multiplication of nuclei in a single cell, which is sometimes absolutely amazing and may go on to the formation of enormous clumps of protoplasm filled with innumerable nuclei. These phenomena are unquestionably the expression of a degenerative cell-proliferation consequent upon the luxuriant growth which has broken through all the bonds of restraint.

Along with these signs of a degenerative growth retrogressive processes of the most extensive character often occur in sarcoma. This is dependent chiefly on the vascular supply of these tumors, and if the latter is insufficient, the tumor-parenchyma undergoes local necrosis. Quite commonly, and in almost all forms of sarcoma, fatty degeneration is found more or less extensively and, it is needless to say, is seen most distinctly in fresh preparations. In large-celled and in giant-celled sarcoma cells are occasionally seen which are crammed full of fat-droplets, and in a stained specimen accordingly present a distinct frothy appearance (Plate 57, Fig. 2). Occlusion of the vessels from thrombosis or embolism may lead to anemic necrosis and caseous degeneration in large portions of the tumor. Microscopically we find in these areas all those phenomena of karyolysis and karyorrhexis that are found in other kinds of infarcted tissues and which have already been described in detail.

The ground-substance may also be the seat of degenerative processes. Occasionally it is found much swollen from edematous infiltration, and mucoid products of metamorphosis are observed; but the change most frequently observed is the deposition of calcium salts, so extensive as to form a deposit of gritty incrustations or lead to extensive petrifactive processes, which usually go hand-in-hand with fatty degeneration in the tumor-parenchyma.

The blood-supply of sarcoma deserves especial consideration. Originally the tumor must, of course, derive its blood-supply from the parent-tissue—that is, from the tissue in which it grows. The oldest vessels are, therefore, preëxisting vessels; but as the tumor grows the vascular system becomes more and more emancipated and the great mass of the blood-vessels in a large sarcomatous tumor must always be regarded as the result of new formation. Sometimes, however, at least in the neighborhood of the vascular trunks, a certain quantity of connective tissue grows along with the vessels and in that case may appear as a well-defined stroma distinct from the true tumor-parenchyma; in other words, a kind of organoid structure takes place in these tumors also, and the expression "histoid" tumor ceases to be applicable.

But most of the blood-vessels have very thin walls, and this is a special characteristic of sarcoma; the vessels are composed entirely of delicate, relatively wide, endothelial tubes in immediate contact with the tumor-cells; indeed, the blood may circulate in cavities bounded exclusively by tumor-cells. It is evident, therefore, that the cells are readily forced apart, and more or less extensive hemorrhages take place, with destruction of portions of the tumor.

The Individual Forms of Sarcoma.—It has long been the custom to classify sarcoma by the form of the constituent cells. From this it is not to be inferred that a sarcoma must be composed only of one particular kind of cell. That is practically never the case. On the other hand, it is usually possible to find a certain type of cell that predominates, or at least makes up the greater mass of the tumor-parenchyma with only slight deviations, or else specially characteristic cell-forms are represented which lend to the tumor a peculiar appearance in the microscopic picture (for instance, "giant-cells"). The tumor is usually named for these predominant histologic features.

It is obvious, however, that there occur in sarcoma an almost limitless array of different forms of cells—just as many as in embryonal or in proliferating juvenile connective tissue in inflammatory growths—and the deviations from normal cell-proliferation which are characteristic of tumor-formation still further multiply the number of forms that the individual elements of these neoplasms may assume. In general it may be stated that the histologic character of the newly formed connective tissue in sarcoma is the more atypical, indistinct, and, as it were, degenerated, the more completely differentiation of the connective-tissue cells is abolished and more embryonal and indifferent is the general character of the cells which appear in the tumor. For this reason the neoplasms which are furthest removed from fully developed continuous connective-tissue complexes and occupy the lowest rank among these tumors are those which are composed exclusively of vascular conglomerations of simple, small, round-cells, such as exist in the body of an embryo as so-called indifferent formative cells; while the highest form, and that which most nearly approaches typical tissue, is the neoplasm in certain parts of which, at least, complete differentiation of a definite connective-tissue group has been affected.

1. **The Round-cell Sarcoma** (*Sarcoma Globocellulare*).—The simplest and, as follows from the foregoing explanation, the lowest type of sarcoma is represented by the so-called round-cell sarcoma, in which the connection between the individual cellular elements is extremely loose or altogether absent. As a rule, two main divisions, the small-celled and the large-celled round-cell sarcoma are made.

In the former group we have tumors which, owing to

PLATE 51.

Large-celled Sarcoma of the Skin (Hemat.-eosin. × 280.): 1, Large polygonal sarcoma-cells; 2, the same with fibrous processes; 3, large connective-tissue trabeculæ; 4, fibrous intercellular substance.

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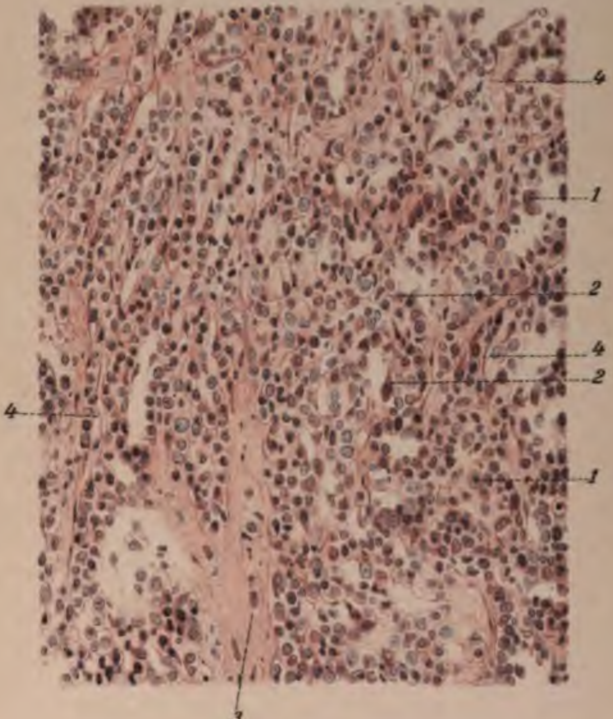
the extremely imperfect connection between their cellular elements, represent macroscopically soft medullary tumors, either whitish gray or grayish red, depending upon the number of blood-vessels present and which, as regards consistence and color, often present the greatest similarity to the fetal brain—a peculiarity from which the old name of "encephaloid" is derived.

The cells that compose this soft parenchyma are small, spheric structures, possessing, as a rule, a narrow, translucent zone of protoplasm surrounding a dark and quite distinctly granulated nucleus. In teased preparations these spheric cells are readily isolated; as a rule, the cells obtained by scraping the cut surface of the tumor at once become perfectly isolated in fluid and can be readily examined (Fig. XXII.). Frequently the nucleus is situated eccentrically,—*i.e.*, very much nearer the cell-wall at one place,—so that the protoplasmic body on direct inspection appears sickle-shaped (Fig. XXII.). The size of the cells is not, as a rule, quite uniform; along with the small, round structures, which correspond perfectly to mononuclear lymphocytes, a few larger spheric forms with dark, dense nuclei occur, which, as regards size and appearance, might be compared to the so-called "myelocytes." Many of the cell-bodies contain fat-droplets. In stained preparations also the texture of these neoplasms appears very simple. The nuclei of the round-cells usually possess great tingibility; the chromatin-structure is dense, almost uniformly granular, and nucleoli are recognized with difficulty. Not infrequently a delicate granular intercellular substance can be traced between the cells, at least in certain areas (Plate 56, Fig. 1); more rarely the intercellular substance is thick enough to form true, delicate fibrils (Plate 59, Fig. 1). The blood-vessels supplying these diffuse collections of cells, which repeat on a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larger scale what we observed in circumscribed areas in so-called "inflammatory small-celled infiltration," are variable in number. As a rule, the larger branches represent mere thin-walled endothelial tubes, around which the masses of round cells are grouped in the form of a mantle in immediate contact with the endothelium (Plate 56, Fig. 1). Sometimes the cellular mass actually penetrates into the lumen; but in regard to the latter point, a caution against artefacts should be given, as they are likely to be formed by the slightest distortion during the removal of the piece of tissue. In such cases the red blood-cells are found among the round tumor-cells, and in this way large hemorrhages may occur, with extensive destruction of tumor-tissue, which manifests itself to the naked eye in a macular appearance of the corresponding portions of the tumor.

It is obvious, in view of the extremely labile structure of these tumors, that their tissues are subject to retrogressive metamorphosis. As soon as the predominance of the proliferating cell-mass over the blood-vessels becomes too great and the nutrition accordingly suffers, portions of the tumor perish. It is probable that a local necrosis is also produced in many cases by the encroachment of tumor-cells on the lumen of the blood-vessels and resulting embolic processes. These necrotic foci are often easily recognized by the naked eye; they appear as large, firm, dry, yellowish foci of radiating structure and variable size, sharply contrasting with the surrounding soft medullary tissue; while microscopically, especially in the marginal zone, all the processes of karyorrhexis and karyolysis, which have been described repeatedly, may be traced. The nuclear débris breaks up near the center of the foci, being reduced to minute, dust-like particles; in the central portions of the tumor the nuclei refuse to take the stain, while the outlines of the cell-bodies often persist for some time. It is needless to say that fatty degeneration is also of frequent occurrence when the blood-supply is deficient. In large portions of the tumor it is often difficult to find a single cell without fat-droplets. The growth

PLATE 52.

FIG. 1.—**Fibroma Sarcomatosum of the Epiglottis** (Hemat.-eosin. × 625.): 1, Large connective-tissue cells with numerous processes anastomosing with one another; 2, fibrous intercellular substance.

FIG. 2.—**Spindle-cell Sarcoma From the Brain** (Hemat.-eosin. × 300.): 1, Spindle-cells cut longitudinally; 2, spindle-cells in transverse section.

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of these neoplasms is usually exceedingly rapid; the cell-production, owing to the complete absence of differentiation and maturation, is exceedingly active; hence, if the tissue is examined in a sufficiently recent state, abundant mitotic figures are found and along with them all the pathologic deviations from the regular type of division which have been described above. The sites of predilection for the development of these extremely destructive tumors are, first of all, the intermuscular connective tissue, the skin, the ovaries, and the testicles. As they encroach upon the surrounding tissue they present a typical example of infiltrating growth, which is particularly recognizable in muscle-tissue, in which the fibers become densely infiltrated and finally melt down, much in the same way as in suppuration, having been forced apart by the cell-invasion, lost their covering of sarcolemma, become infiltrated in columns, and finally stuffed full of the round tumor-cells (Fig. X.).

From a morphologic standpoint the so-called "*lymphosarcoma*" is closely related to the small round-cell sarcoma. It has its origin in lymph-nodes, in the lymphatic tissue of some of the mucous membranes, and sometimes in the spleen. Unlike the round-cell sarcoma, it possesses a readily demonstrable, true fibrous stroma, with branching, stellate connective-tissue cells, which send out their processes between the round-cells or groups of round-cells. In this form of tumor we have, therefore, a reticular supporting tissue which corresponds in every respect to the "cytogenic" tissue of the lymphatic apparatus. This supportive tissue lodges the nutrient vessels. Sometimes

Tab. 52.

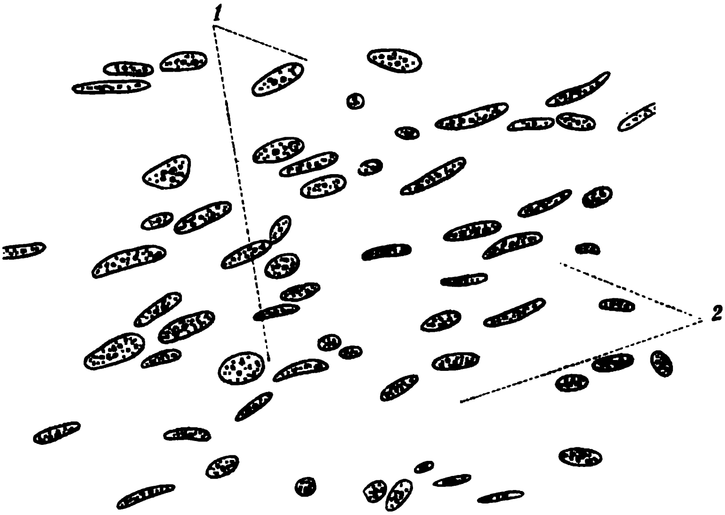
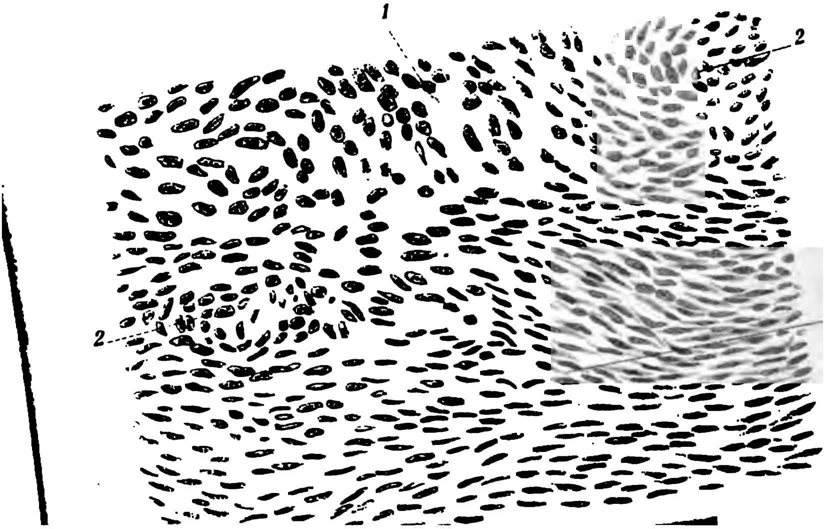


Fig. 1.



the supportive substance is so abundantly developed that the tumor becomes harder, and we then have the so-called "*lymphosarcoma durum.*"

It is evident that a partial and local increase of this reticulum in the neighborhood of blood-vessels must result more and more in the formation of an "alveolar structure," and, as a matter of fact, forms are often seen which, in the point of alveolar arrangement, present the greatest similarity to carcinoma. This similarity is enhanced by the fact that sarcoma of this character, as a rule, is not of the small round-cell variety, the cellular elements being larger, richer in protoplasm, flattened and polygonal on account of being densely packed together, and thus simulating a true epithelial aggregation. Owing to this morphologic similarity to the type of the carcinoma and the resulting diagnostic difficulties the term *sarcoma carcinomatodes* has often been employed to describe this form; but the name ought to be sedulously avoided whenever it is possible to obtain information in regard to the real character of the tumor. Usually such information is obtained by careful analysis of the contents of the individual alveoli and their relations to the surrounding stroma. In alveolar large-cell sarcoma the cells have become more polymorphous. In addition to the simple round forms, numerous elongated, polygonal structures, provided with protoplasmic processes are seen, particularly in the peripheral portions of the alveoli, and, as a rule, a connection between these cellular processes or intercellular substance, if such is present, with the fibers of the reticulum that form the alveolar walls, can be demonstrated; the fibrous tissue of the alveolar walls may send out delicate, extremely minute filaments to form an intercellular substance. The individual alveoli themselves are unequal in size and usually spheric, in contradistinction to the cylindric cell-aggregations of carcinoma.

2. **Spindle-cell Sarcoma** (*Sarcoma Fusicellulare*).—In spindle-cell sarcoma we see a higher degree of cell-differentiation than in round-cell sarcoma. While the physiologic prototype of the latter is practically represented by

PLATE 53.

FIG. 1.—**Fibroma Sarcomatosum of the Inguinal Glands** (Recent Teased Preparation. × 280.): 1, Large spindle-cells imbedded in fibrous intercellular substance; 2, isolated spindle-cells; 3, spindle-cells with their cell-bodies in a state of partial fatty degeneration.

FIG. 2.—**Spindle-cell Sarcoma of the Uterus** (Hemat.-eosin. × 250.): 1, Long, spindle-shaped cells; 2, segments of the same without nuclei; 3, cells with stellate protoplasmic processes.

FIG. 3.—**Sarcoma Myxomatosum from the Brain** (Hemat.-eosin. × 250.): 1, Cells after the type of round cells; 2, spaces filled with mucoid ground-substance; 3, thin-walled blood-vessel.

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the so-called small-cell inflammatory infiltration, the elements of the spindle-cell sarcoma find their prototype in the "fibroblasts," which, as we have seen, may play an important part in inflammatory proliferations and in regeneration.

In this variety, then, the connective-tissue character is more pronounced even in the form of the cells. The development of intercellular substance is variable; the tissue may present a distinctly fibrous type, and it may be so abundant as to bring about transitional forms between spindle-cell sarcoma and the cellular form of fibroma.

According to the average size of the cells, these tumors are divided into small and large spindle-celled sarcomata. In the former the individual cells are small in size, and in a recent preparation readily isolated, appearing as elongated structures with a central bulging and long processes drawn out into points, which project from each end of the cell. The nucleus is situated centrally in the thicker portion of the cell; the shape is that of a long ovoid, and the chromatin network is quite thick. The nuclei usually occupy the entire width of the cell, so that in a longitudinal section the body-protoplasm appears in the form of two peaked caps covering the two poles of the nucleus. The mutual arrangement of the cells is such that the point of one cell is inserted into the space between two other cells, thus bringing about a rhomboid arrange-

Tab. 53.

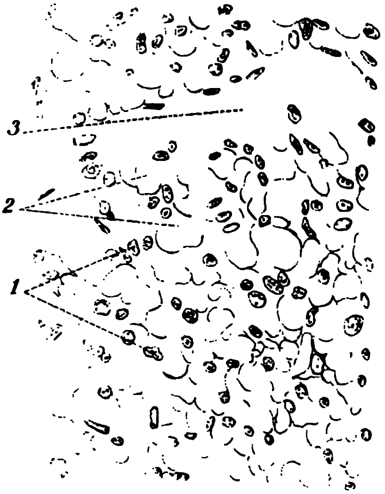
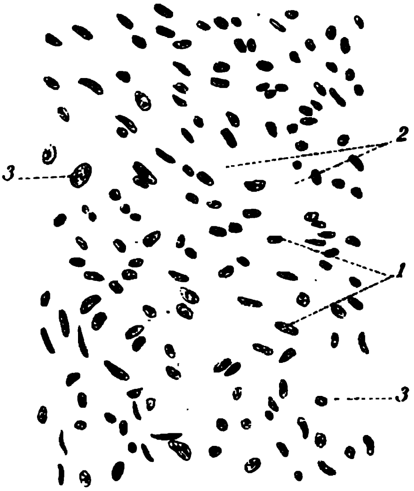


Fig. 3.



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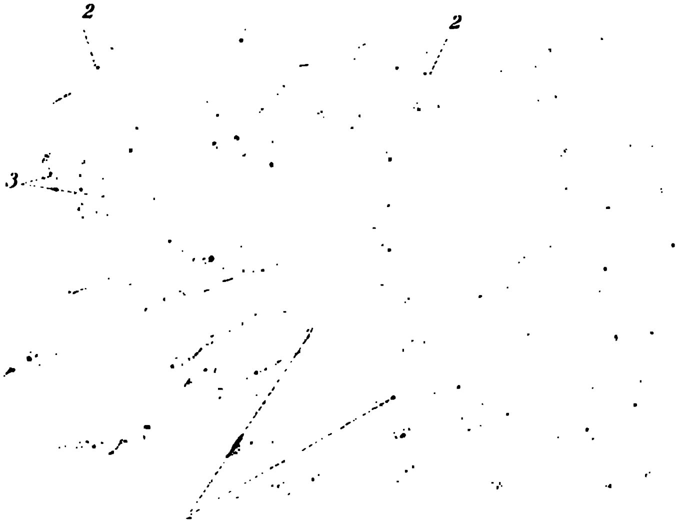

ment and permitting the cells to be densely crowded together. This picture is, of course, seen only in longitudinal sections of the cell-cords. As only a few of them are, as a rule, arranged in parallel rows, and as they are usually made up in bundles, the individual bundles, which vary much in thickness, may interlace with one another in every conceivable direction.

In a large cross-section we, therefore, see every conceivable section of the cell from the completely longitudinal to the completely transverse direction, the latter, of course, giving the impression of simple round-cells, with which they may readily be confounded (Plate 52, Fig. 2). This interlacing of the fasciculi also produces a certain resemblance to myoma, except that the nuclei of the spindle-cells in longitudinal section never present the simple rod-shape. Sometimes there is a definite relation between the cell-cords and the blood-vessels, in the sense that the latter are enveloped as by a mantle by the cell-spindles arranged lengthwise, so that in the neighborhood of cross-sections of blood-vessels the adjoining tumor elements also are seen in transverse section. The latter, however, are separated from the lumen of the blood-vessel by a distinct endothelial tube, whereas those forms in which a direct transition from endothelial cells to tumor-cells is observed, while the blood circulates freely in canals, are to be classified as endotheliomata.

In the large spindle-celled sarcoma a somewhat greater variation is observed in the cell-forms. The individual cells contain more protoplasm. The nucleus does not occupy the entire width of the cell, but is also larger and less linear. In addition to the simple spindle-cells there are forms with several sharp or blunt, club-shaped processes and even some genuine stellate figures. The processes are often longer, sometimes very delicate, and lose themselves in the intervals between the neighboring cells; occasionally they even present dichotomous branching; true intercellular substance is scanty, if, indeed, any at all is demonstrable. It is needless to say that the mutual arrangement of the cells is accordingly less regular and fascicular than in the small spindle-celled sarcoma, and in most examples a certain modeling of the cells from mutual pressure may be observed (Plate 53, Fig. 1).

Fibrosarcoma approaches the small spindle-celled sarcoma as regards the development of its individual cellular elements. It is characterized by an unusually distinct development of the interstitial substance. In this form also the cells are usually small and spindle-shaped, with a granular protoplasm and vesicular nuclei (Plate 53, Fig. 3; Plate 52, Fig. 1); but the cellular processes are drawn out into delicate fibers which anastomose with one another and enter into communication with fibers situated between the cells and not in immediate relation with the same, probably representing excretion or cleavage products of the cells. Occasionally the cell-bodies and their fibrous processes exhibit a branching, net-like arrangement ("net-cell sarcoma," Plate 52, Fig. 1). Among these elements roundish nuclei are scattered about, which appear to pass into fibers without the intervention of the protoplasmic body (so-called "nuclei fibers").

Fibrosarcoma is distinguished from simple fibroma by the number of cells, the abundant amount of protoplasm, and the polymorphous character of the cells.

Sometimes the fibers both in fibrosarcoma and in fibroma undergo swelling and a true mucoid metamorphosis, which usually involve the cell-bodies also, giving us *fibrosarcoma myxomatosum*. In stained sections of these tumors (Plate 53, Fig. 2) we see a network of fibers with broad circular meshes filled with mucoid substance, and between these meshes vesicular roundish or oval nuclei, around which it is impossible to demonstrate any protoplasmic body, and which appear to be denuded nuclei scattered among the fibers.

3. **The Giant-cell Sarcoma** (*Sarcoma Gigantocellulare*).—The giant-cell sarcoma derives its name from the giant-cells which it contains in greater or less abundance, although the term is not intended to signify that the tumor is entirely composed of such cells: they are merely scattered about here and there.

A giant-cell, it is needless to say, is a cellular individual with several nuclei; we have already met this type of cell in many forms of inflammation and regeneration, as well as in the infectious granulomata.[1] While the actual presence of several nuclei is a *sine quâ non* in the definition of a giant-cell (hence also the name of "polykaryocyte"), these structures are evidently produced in a variety of ways, and this variable genesis is often clearly expressed by their form. The giant-cell is in the main produced in one of two ways: by continuous division of the nuclei in the same cell ("proliferation giant-cell") and by the fusion of preëxisting cells ("conglutination giant-cell"). Furthermore, it has been seen that in tuberculosis, for example, giant-cells may be formed from the cells of vessels, either by the fusion of endothelial cells derived from blood- and lymph-vessels, or from homogeneous, degenerated contents of blood-vessels (hyaline capillary thrombi).

The production of giant-cells is peculiarly associated with foreign bodies of every kind ("foreign-body giant-cells"); they are seen, therefore, after the invasion of the tissue by all kinds of corpuscular elements (hairs, suture material, dust-particles, bacteria); but they may also be formed around necrotic portions of the tissue itself, which act as foreign bodies (for example, horny particles in squamous epithelioma). These foreign-body giant-cells are to be distinguished from the "parenchyma giant-cells," so called by von Hansemann, which may be produced in a variety of ways in tumors. The enormous number of nuclei which these giant-cells sometimes contain, and, on the other hand, the extreme scarcity of mitotic figures in the cells appear to suggest that some of the nuclei at least have been produced without mitosis by direct division of fragmentation. This theory is supported by the buds that are sometimes observed in the nuclei and by the fact that two or three nuclei are often found in the same cell, still connected by bridges of chromatin substance.

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[1] Even among tumors the occurrence of giant-cells is not by any means confined to the sarcoma; they also appear in endothelioma, in carcinoma, and even in adenoma.

PLATE 54.

FIG. 1.—**Polymorphocellular Sarcoma of the Nose with Distinct Intercellular Substance** (Hemat.-eosin. × 280.): 1, Large polygonal tumor-cells with vesicular nuclei; 2, fibrillar cellular processes; 3; fibrous intercellular substance.

FIG. 2.—**Large-cell Sarcoma from the Mesentery** (Hemat.-eosin. × 280.): 1, Polygonal tumor-cells with vesicular nuclei; 2, broad connective-tissue septa; 3, delicate strands of fibrous intercellular substance.

Finally, it is well known that under normal conditions multinuclear cells are found in growing as well as in atrophic bone (osteoblasts and osteoclasts), and the red bone-marrow at all times contains giant-cells. This type of giant-cells, called "*myeloplaxes*," is evidently the one that is especially reproduced in sarcoma which grow from the skeletal system, both from the periosteum and from the marrow (periosteal and myelogenic sarcoma); it is in this form of sarcoma that multinuclear cells are usually found in greatest abundance, and they, therefore, furnish the largest contingent of true giant-cell sarcomata.

The arrangement and distribution of the nuclei are extremely variable. Sometimes they are found congregated at one pole, or more frequently at the two opposite poles, of the cell, while the intervening portion is free from nuclei (polar, bipolar nucleation); or the nuclei are arranged in a ring- or girdle-shaped zone at the periphery of the cell, so that in transverse section an almost continuous wreath of nuclei is seen surrounding an absolutely homogeneous center. Cells with this disposition of the nuclei belong to Langhans type of giant-cell, the cell especially characteristic of tuberculosis, but is also observed in other lesions. Weigert attributed this arrangement to an antecedent caseous necrosis of the cell-body. On the other hand, the so-called myeloplax type of giant-cell is the one that usually presents the peculiarity of having the nuclei congregated in dense masses in the inner portions of the cell-body, the periphery of the cell forming a pale zone devoid of nuclei. Far from being

Tab.54.

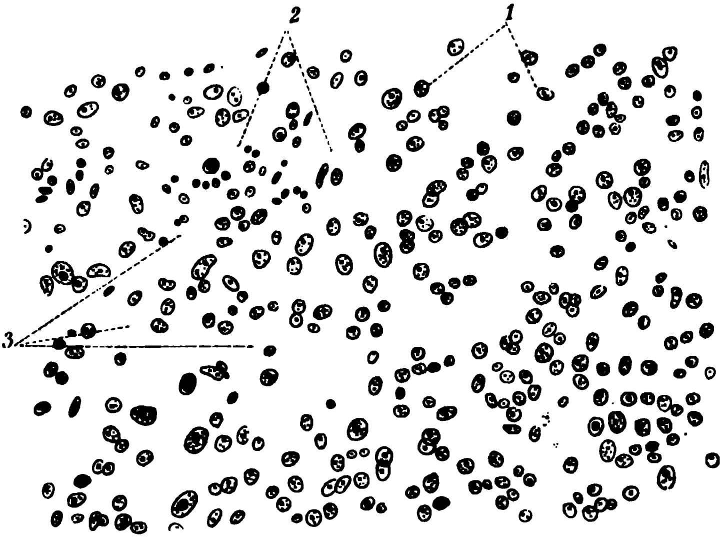
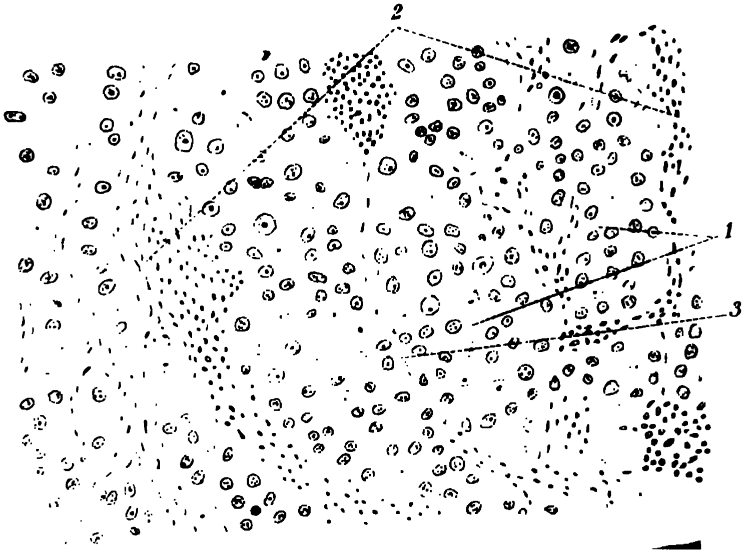


Fig.1.



invariably regular and vesicular, the nuclei, both within the giant-cells and outside of them in other cells of the same tumor, frequently assume abnormal forms, particularly as regards size and quantity of chromatin. Very large nuclei are seen, which many times surpass their neighbors in extent—so-called giant-nuclei, which have already been referred to in another place. Quite often they also possess an irregular, lobulated structure, and the chromatin is generally of unusual density.

In these examples it looks as if an attempt has been made at multiplication of the nuclei by direct division or by gemmation, but that the attempt has not proved successful. Sometimes these giant-nuclei present the most bizarre division or fragmentation figures, producing remarkable roset shapes and giving the impression as if a large lump of chromatin had suddenly burst as a result of internal pressure, numberless minute fragments being scattered in all directions. True hollow nuclei, which, on transverse section, appear as circular figures are also observed. It is comparatively common to find in giant-cell sarcoma, in addition to the nuclear conglomeration, a great variety of cell-inclusions. Thus the leukocytes as well as other dead cells may be found incorporated in the protoplasm. It is possible that these structures act as foreign bodies and cause the production of giant-cells in the same way as described in connection with foreign bodies invading the tissue from without. The number of nuclei in a single giant-cell is sometimes so enormous, and the structures are sometimes so large, that they are not infrequently discernible macroscopically as dark points in a section; in serial sections several hundreds of nuclei are sometimes counted in a single cell.

The protoplasm of giant-cells is usually soft and perishable, and is peculiarly prone to fatty degeneration. In hardened and stained sections the cell-bodies accordingly appear perforated, like a sieve, by the vacuoles which were originally filled with fat-droplets (Plate 57, Fig. 2); the outline is irregular and sinuous, and the structure of most of that part of the cell which is devoid of nuclei

PLATE 55.

FIG. 1.—**Perithelioma (So-called Angiosarcoma) from the Leg** (Hemat.-eosin. × 60.): 1, Blood-spaces in transverse section; 2, proliferating perithelial cells surrounding the vessels like a mantle; 3, blood-pigment within the tumor.

FIG. 2.—**Perithelioma (So-called Tubular Sarcoma) of the Liver** (Hemat.-eosin. × 95.): 1, Blood-vessels; 2, dense aggregations of large round-cells around the blood-vessels; 3, strands of connective tissue.

PLATE 56.

FIG. 1.—**Details of the Preceding** (× 320.): 1, Small blood-vessels; 2, surviving endothelial cells; 3, proliferated perithelial cells.

FIG. 2.—**Hemangioendothelioma (Cylindroma) of the Parotid Gland** (Hemat.-eosin. × 280.): 1, Proliferated endothelial cells; 2, walls of blood-vessels in a state of hyaline degeneration.

FIG. 3.—**Alveolar Large Round-celled Sarcoma from the Periosteum** (Hemat.-eosin. × 250.): 1, Heavy septum of connective tissue; 2, delicate connective-tissue reticulum; 3, polyhedral cells with vesicular nuclei.

PLATE 57.

FIG. 1.—**Periosteal Round-cell Sarcoma from the Skull** (Carmin. × 280.): 1, Fibrillar connective tissue from the periosteum; 2, blood-vessels: 3, dense mass of round-cells.

FIG. 2.—**Round-Cell Sarcoma from the Lower Jaw (Epulis Sarcomatosa)** (× 250.): 1, Giant-cell with many nuclei; 2, fat-vacuoles within the same; 3, polyhedral cells.

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resembles honeycomb or soapsuds. This is particularly the case when the section, as, of course, often happens, involves only the outer portion of a cell, where there are no nuclei (especially the upper or the lower) and where the vacuoles are thickest (Plate 57, Fig. 2).

The remaining cells of giant-cell sarcoma may be of various kinds. Most frequently the tumor conforms to the type of the large round-celled sarcoma or the spindle-cell sarcoma, and in almost every instance the uninuclear cells considerably exceed in number the giant-cells. Fibrillar processes (so-called pseudopod-like processes) such as we have seen in the giant-cells of tubercle, and

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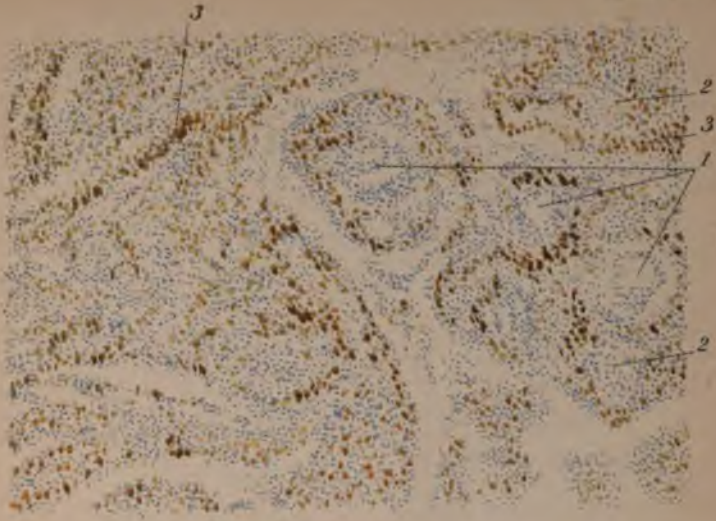

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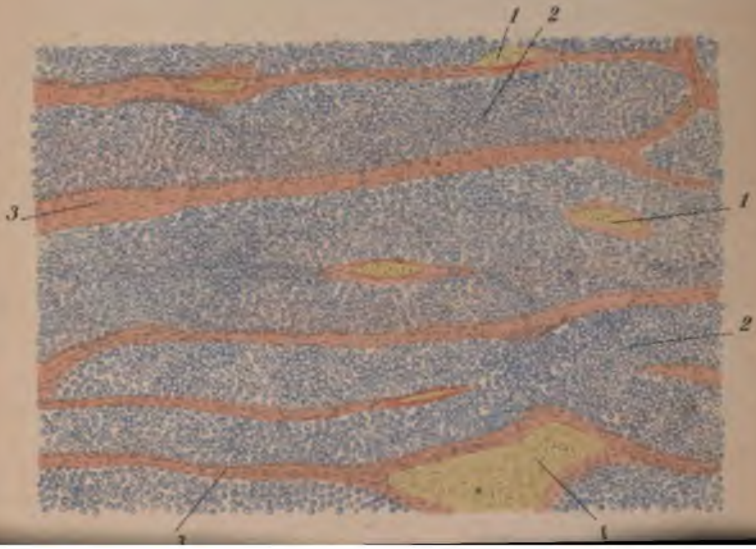

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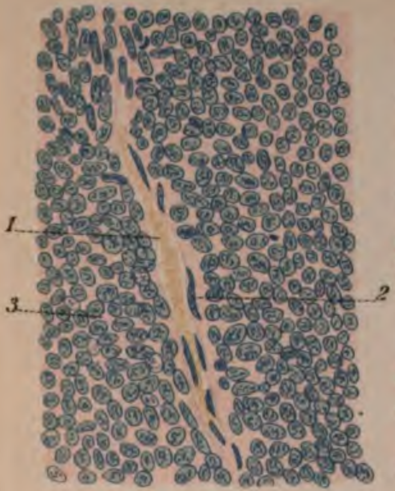

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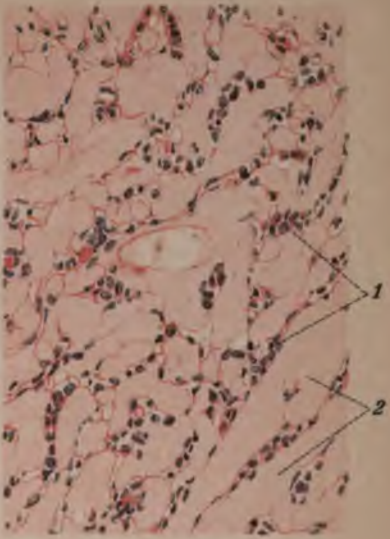
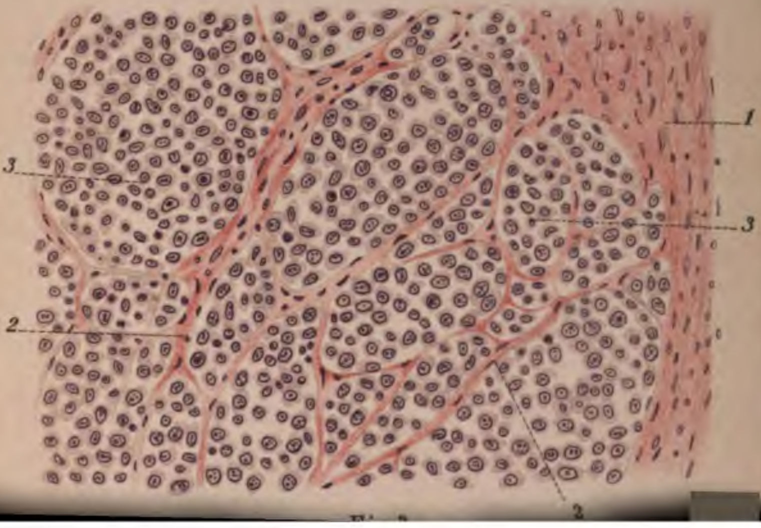


Fig. 2.



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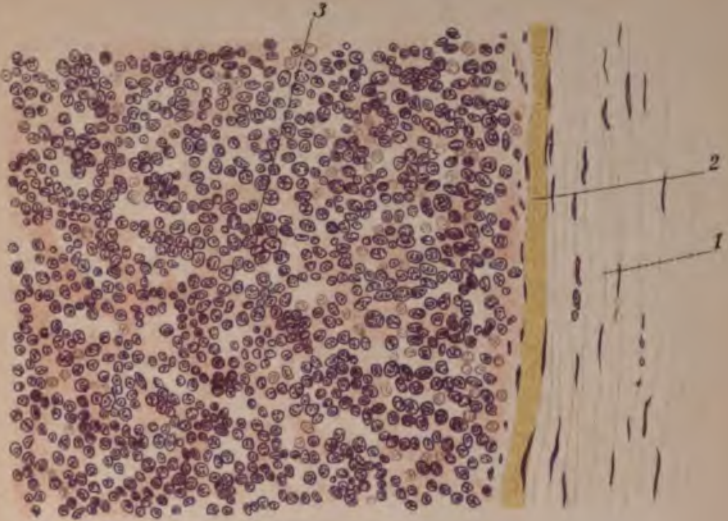

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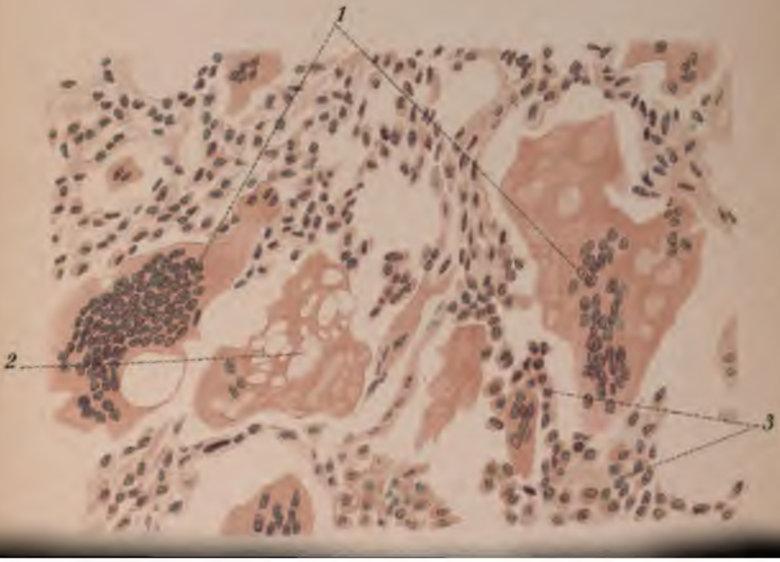

which are connected with the remaining cellular material, are seen only exceptionally in sarcoma. As observed, most giant-cell sarcomata have their origin in the skeleton; the jaws appear to possess a special predilection for the development of these tumors, which in that situation have been designated by Nélaton *epulis.* (For purposes of greater accuracy the term "epulis sarcomatosa" is also used.)

A large number of sarcomata cannot be classified with any of the forms so far described, as the constituent cells present many differences, both among themselves and as a whole, and cannot be characterized as round-cells nor as spindle-cells, nor even as giant-cells; as a rule, they are irregularly polygonal elements, and scattered through them in varying numbers are large and small spheric and spindle-shaped forms, so that it is impossible to find a uniform cell-type. Sometimes one form predominates and sometimes another; multinuclear and even true giant-cells may be represented. Owing to this variety in the cells in a small area of the tumor they are best summed up under the name of *polymorphocellular sarcoma.* It is hardly necessary to say that the arrangement of the cells with regard to one another is also extremely variable. It depends, in the main, on the degree of development of the interstitial substance. In many cases it is sparingly developed and consists solely of cellular processes which vary more or less in length and are connected with one another or vanish among the cell-bodies (Plate 54, Fig. 1, and Fig. XVIII.). As a rule, the processes are seen better in a fresh preparation after isolation by teasing than in a stained section. Sometimes the cells are arranged in groups and framed in genuine fibrous tissue, thus producing a distinct alveolar structure (Plate 52, Fig. 2). A definite relation to blood-vessels is sometimes made out, the cells being grouped around the vessels in tube-like aggregations, and in a sense presenting an enormously thickened adventitial layer. Owing to the similarity of the tumor-elements to epithelial cells flattened by mutual pressure these sarcomata have often been designated *epithe-*

FIGURE XVII.

Alveolar Sarcoma (× 320.): 1, Large tumor-cells connected in nest-like aggregations and in part possessing very extensive nuclei; 2, broad connective-tissue septa; 3, delicate fibrous intercellular substance, continuous with the septa; 4, atypical mitotic figures in the tumor-cells.

FIGURE XVIII.

Polymorphocellular Sarcoma of the Upper Jaw (× 320.): Spindle and stellate cells; among them multinucleated cells; protoplasmic bodies loaded with fat-droplets.

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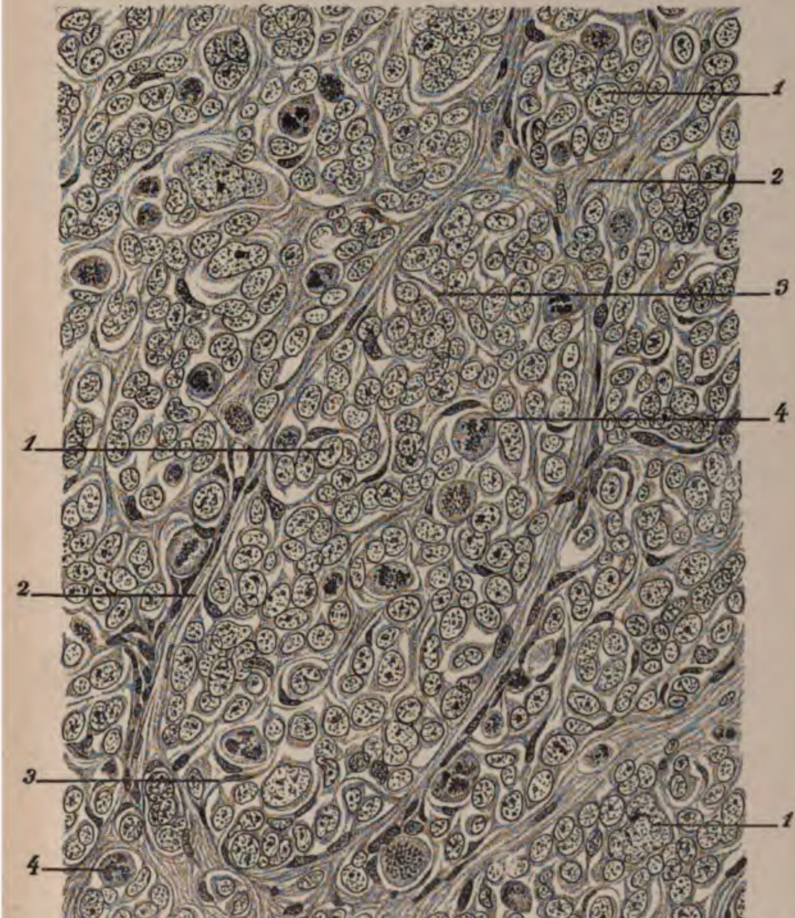
lioid-cell sarcomata; but it is to be remembered—as has already been pointed out in the introduction to the subject of tumors—that originally the word epithelioid, according to Virchow, was not intended to designate cells of a definite form, but rather cells connected with one another in a manner similar to that of epithelial cells.

Many sarcomata present not only proliferation of numberless cells of a definite form or of several different forms, but also, in part at least, the development of tissue belonging to the connective-tissue group. This result may be brought about in one of two ways: either a typical connective-tissue tumor, belonging to the group that has been described, secondarily undergoes metaplastic, irregular, atypical cell-proliferation, which does not lead to the production of fully formed, mature tissue, but becomes arrested at some lower embryonal stage of development. This process was formerly called "sarcomatous degeneration." We then have a combination characterized by a secondary change of growth, metaplasia—a decadence, as it were, of the tumor and its return to a primitive stage. In the other case the formation of a typical, mature tissue goes on at the same time hand-in-hand with the unbridled proliferation of undifferentiated cellular individuals, so that a combination of two kinds of tumors is present from the beginning.

After the explanation that has been given it would be improper to apply the same term to these two varieties of a combination of tumors composed of different tissues or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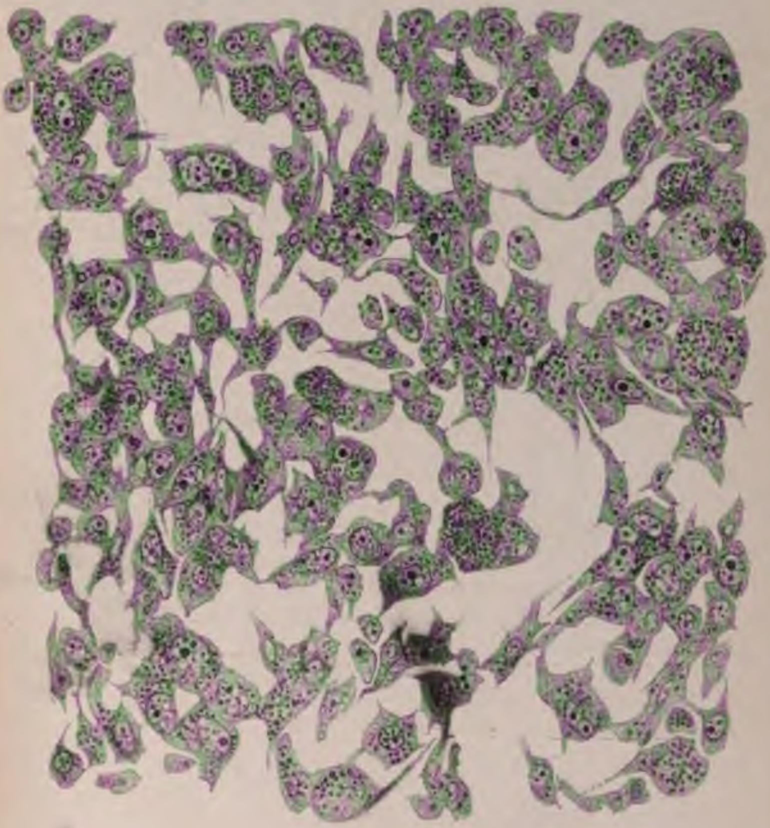

Fig. XVIII.

representing at least different degrees of differentiation of the same tissue. Again we shall follow the nomenclature first laid down strictly by von Borst. Accordingly, if a neoplasm which has originated in a typical mature tissue becomes atypical by a change in the character of proliferation of the cells, we shall use the noun of the corresponding tumor and add to it the adjective "sarcomatosum." We, therefore, speak of a fibroma, myxoma, etc., "sarcomatosum"; while the compound words made up of the nouns indicating two different tumors, such as fibrosarcoma, myosarcoma, and so on, are reserved for those forms in which the tumor clearly shows the combined growth of two different tissue varieties from the beginning.

It is evident that such a commingling of various kinds of cell-complexes, in whatever way it may have been brought about, must eventuate in a richer development of structure; hence the term "histoid" cannot well be applied to such tumors, although in the final analysis elements belonging to the connective-tissue group enter into their composition. The development of these elements, however, is so multiform that even at the first glance the contrast between indifferent cells and fully formed and "physiologically finished" tissue is clearly visible, thus suggesting a comparison with the structure of a fully formed organ. The irregular, undifferentiated masses of cells play the part of parenchyma, while the mature tissue represents the supporting substance, so that the composition of tumors of this kind may well be called "organoid."

In the description of fibroma it was pointed out that the occurrence of an abundant cell-proliferation, in which individual cells no longer attain the type of the adult connective-tissue cell, may alter, at least partially, the character of the tumor, and compel the use of the term *fibroma sarcomatosum*. The unfinished islands of cells are usually composed of large spindle-cells with abundant protoplasm, such as are not found in adult connective tissue, but at most are seen as fibroblasts in quite juvenile tissue. Polygonal or spheric cells may also

FIGURE XIX.

Myxosarcoma from the Jaw (× 280.): 1, Cell-cords consisting of polygonal cells with processes; 2, large cells with abundant protoplasm and numerous processes; 3, intercellular fibrillar connections.

FIGURE XX.

Liposarcoma from the Peritoneum (× 80.): 1, Fatty tissue with multiplication of cells; 2, greatly proliferated cells containing fat; 3, connective-tissue stroma.

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occur, but the ground-tissue is always fibrocellular and thus shows the original type of the tumor. On the other hand, the term *fibrosarcoma* indicates a tumor in which, from the beginning, the development of fibers, on the one hand, and of large spindle-shaped cells, on the other hand, has gone on side by side (see *supra*). If net-like branching elements, between the processes of which is seen a mucoid intercellular substance, make their appearance, we have a *myxosarcoma;* whereas, according to our explanation, a sarcomatous tumor, parts of which secondarily undergo mucoid softening, should logically be called a sarcoma myxomatosum. Myxosarcoma, in contradistinction to simple sarcoma, contains numerous large branching cells; sometimes the mucoid deposit is especially well developed in certain portions of the tumor, while in other portions round, spindle, or polygonal cells predominate.

A special combination that is rarely seen is *liposarcoma.* In this variety we have a proliferation of fatty tissue, with here and there a more or less extensive proliferation of juvenile, not distinctly differentiated, cells. The fatty tissue presents itself, just as in a typical lipoma, in the form of large spheric cells arranged in large conglomerations like bunches of grapes, with peripheral, usually sickle-shaped or cup-shaped, nuclei; but even the more cellular portions may reveal a marked tendency to fatty infiltration. The individual cell in this variety also is spheric in shape, but possesses a large vesicular nucleus, usually situated in the middle of the cell, while numerous fat-droplets are distributed throughout the protoplasm, and, as they are dissolved out in the stained preparation,

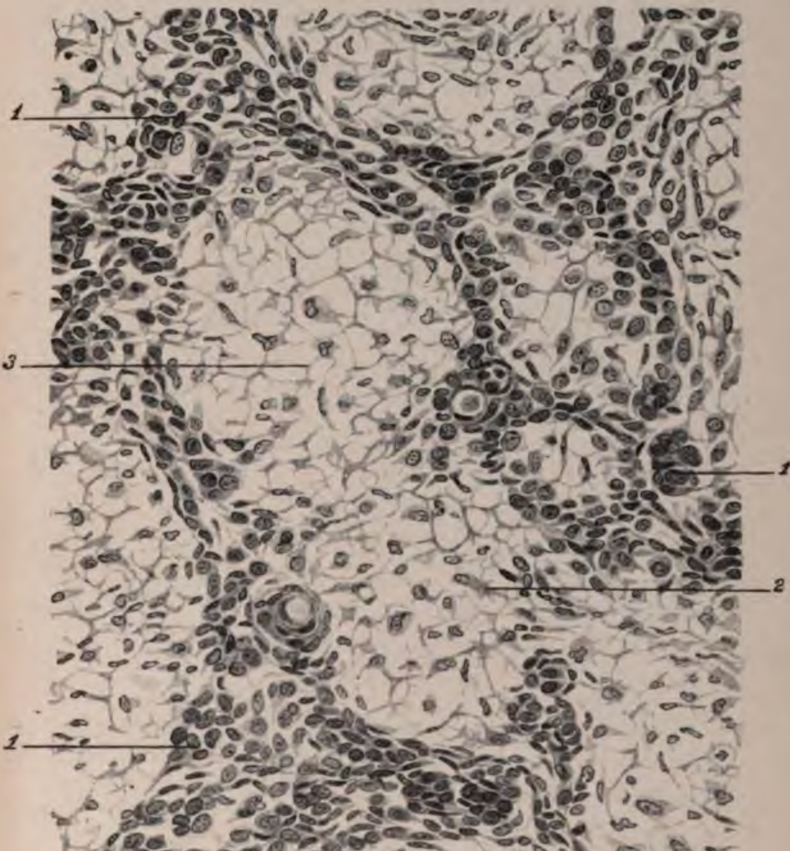
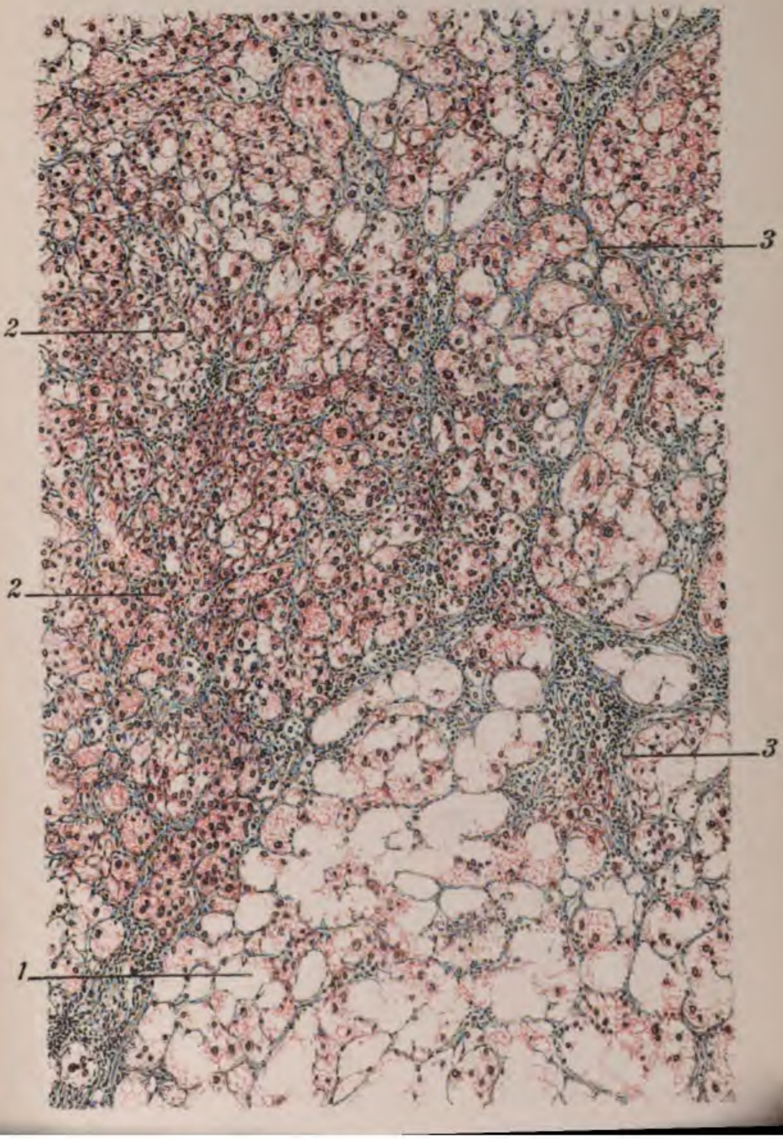


Fig. XIX.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the cells assume a vacuolated structure resembling soapsuds. This primary formation must not, of course, be confounded with fatty degeneration occurring in sarcoma cells, which, as mentioned, may be met in any form of sarcoma. As a result of the commingling of fat-cells and protoplasmic cells that are also infiltrated with fat liposarcoma is a yellowish-white tumor resembling paraffin; it is sometimes multiple, as, for example, in the peritoneum, where it may appear in the form of innumerable small nodules (personal observation) (Fig. XXI.).

Combinations of sarcoma with cartilaginous tissue, on the other hand, are observed much more frequently. Sometimes the development of the cartilage is quite typical in places, showing that the sarcoma has grown along with the cartilage, and such tumors should receive the name of *chondrosarcoma.* The cartilaginous substance presents well-developed capsules, and within them, as in a simple chondroma, one or several cartilage-cells. These areas are usually circular or cylindric in shape, and bounded by extremely cellular tissue, made up of spindle-cells arranged in parallel rows, which in a sense play the part of perichondrium. Adjoining this is a true sarcomatous tissue in which the formation of the cells is more manifold; occasionally giant-cells are represented. It is undeniable that even in these genuine combination-forms a certain atypical character sometimes manifests itself in the development of the cartilage-tissue, the capsules being insufficiently developed and the cavities often reduced to a mere cleft or containing large cellular accumulations.

It is even more common to see in a tumor which was originally cartilaginous an extensive multiplication of cells, with disappearance of the intercellular substance; metaplastic processes take place in the cartilage-cells, ending finally in complete cellular metamorphosis of the entire cartilage and producing the *chondroma sarcomatosum.* As the cartilage-cells continue to develop and their protoplasmic bodies swell, the cavities expand and the ground-substance is dissolved. In this way cellular islands surrounded by remains of cartilage are formed, which

PLATE 58.

FIG. 1.—**Chondroma Sarcomatosum from the Jaw** (Hemat.-eosin. × 70.): 1, Cellular portions consisting chiefly of spindle-shaped elements; 2, cartilaginous substance with spaces containing several cells; 3, calcified cartilaginous substance.

FIG. 2.—**Osteoid Sarcoma of the Mamma** (Hemat.-eosin. × 320.): 1, Blood-vessels within structures resembling medullary cavities; 2, polygonal cells with vesicular nuclei; 3, osteoid substance.

PLATE 59.

FIG. 1.—**Lymphosarcoma of the Mediastinum** (Hemat.-eosin. × 300.): 1, Blood-vessel; 2, round-cells proliferating into the vessel-wall; 3, diffuse aggregations of round-cells; 4, delicate fibrillar intercellular substance.

FIG. 2.—**Polymorphocellular Sarcoma with Giant-cells from the Brain** (Carmin. × 300.): 1, Spheroid cells with vesicular nuclei; 2, cells with giant nuclei; 3, multinuclear cells (giant-cells); 4, giant-cells into which leukocytes have penetrated; 5, so-called giant-mitoses; 6, giant-cell with numerous fat-vacuoles into which leukocytes have penetrated.

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vascularized from the sarcoma-tissue and enlarge by sending out vascular buds and cell-cords into the surrounding tissue in such a way as to form a structure resembling medullary cavities. The lacunæ in the cartilage are opened and become filled with cells, or the cells within the cartilage-cavities, which have already undergone proliferation, mingle with the sarcoma elements. Quite frequently the cartilaginous portion of these tumors undergoes partial calcification. This begins usually in the capsules of the cartilage-cells, where circular calcareous deposits are formed which subsequently extend into the ground-substance and present jagged areas bounded by irregular outlines. As in a simple chondroma, so in chondrosarcoma, softening of the ground-substance with mucoid change and the formation of myxomatous areas, or even more advanced stages of softening with the production of cystic cavities, may take place.

Sarcoma characterized by the simultaneous development of osseous substance usually is termed *osteosarcoma;* but

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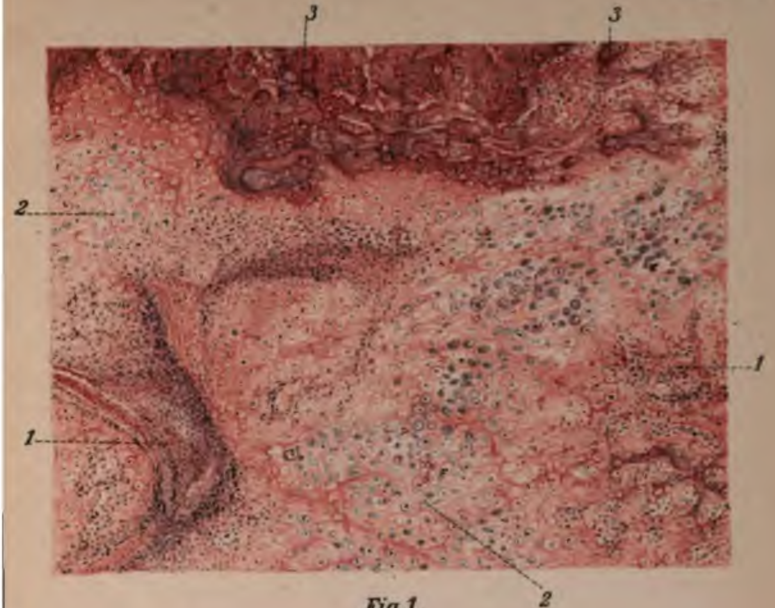

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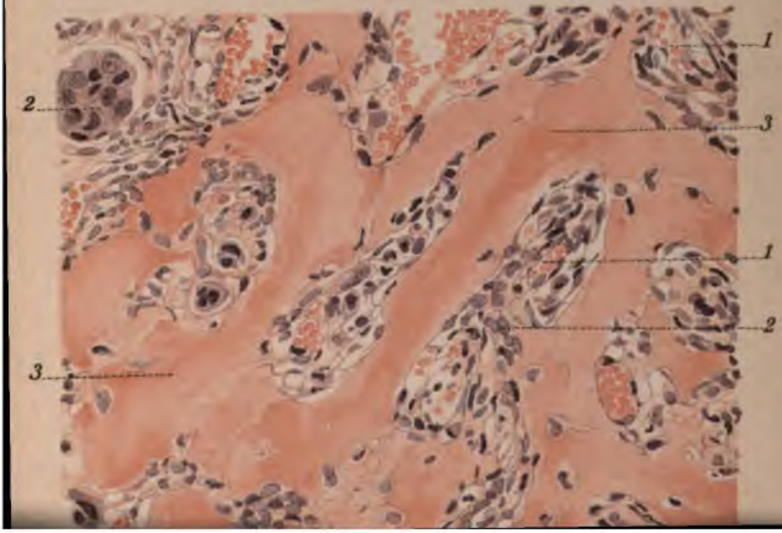

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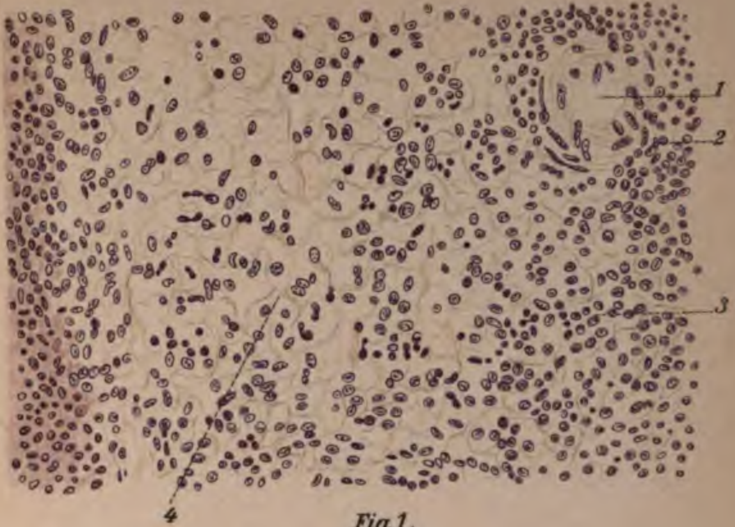
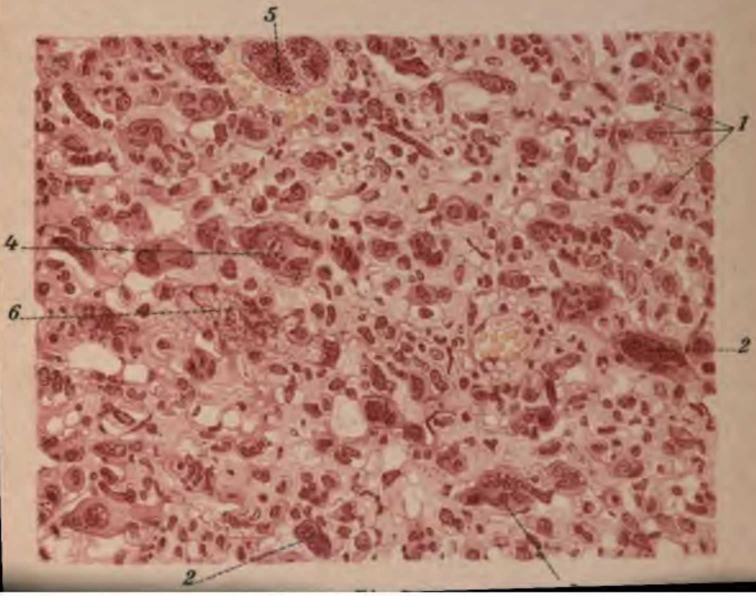


Fig. 1.



this term is also often used improperly, and it is important to distinguish between a great many possibilities. In the first place, not every sarcoma that has its origin in bone may be labelled an osteosarcoma. The periosteum frequently gives rise to a spindle-cell or sometimes a round-cell sarcoma, which, as it enlarges, of course exerts a destructive influence on the bone-substance and gradually brings about—in a manner more fully described later—solution and removal of the bone. Hence these tumors at different stages of their development possess more or less abundant masses of bone which represent their stroma, and which are furnished by the tissue immediately contiguous to the part of origin. These masses of bone are gradually consumed and ultimately disappear altogether. Again, metastatic nodules derived from sarcoma that has developed in some of the soft parts may reach the bone and continue to grow within the bone; but it obviously would be altogether improper to designate such a tumor osteosarcoma, as is sometimes erroneously done. Such a tumor is not an osteosarcoma, but a "sarcoma of bone." During the growth of such tumors within the bone inflammatory reaction may appear in association with osteophytic proliferation and the formation of new bone; and as the development of the latter is often abundant and contributes materially to the increase of the tumor-mass, it may, in a given case, be exceedingly difficult, if not impossible, in a single preparation, to decide the question whether the osseous new formation is to be regarded as an inflammatory proliferation of the preëxisting bone or a product of the tumor itself.

It has been shown (under Osteoma and Fibroma) that true ossification, or processes extremely similar thereto, may occur in different kinds of connective-tissue tumors. In the same way such processes may establish themselves in sarcoma, and we then have, as a parallel to ossifying fibroma, *ossifying sarcoma.* The development of bone-substance in such tumors is often defective in a great many respects. Between the complexes of polygonal, spindle-shaped sarcoma-cells the ground-substance

FIGURE XXI.

Ossifying Sarcoma of the Jaw (× 70.): 1, Cellular tumor-tissue, consisting principally of spindle-shaped elements; 2, bone-substance with stellate bone-cells; 3, rows of osteoblasts; 4, giant-cells which act as osteoblasts.

FIGURE XXII.

Lymphosarcoma of the Inguinal Lymph-glands (Recently Isolated Cells. × 300.): 1, Small round-cells; 2, large round-cells with an abundance of protoplasm; 3, fat-containing cells; 4, red blood-cells.

FIGURE XXIII.

Multiple Myeloma from the Ribs (Freshly Isolated Cells. × 300.): Large round and polygonal cells, with one to two nuclei; scattered among them, red blood-corpuscles.

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a homogeneous, glistening mass, distributed in trabeculæ and retiform structures, and containing only a few survivors of the cells which had originally occupied the spaces; these are usually elongated and spindle-shaped (Plate 58, Fig. 2). Sometimes these cells have a more irregular outline, or they may exhibit lateral, delicate, fibrillar processes, by means of which they may even anastomose with one another. While, therefore, the cells possess the greatest similarity to genuine bone-corpuscles, the corresponding development of ground-substance is missed. The characteristic lamellation and calcification never take place, and the substance resembles more the matrix of cartilage. These tumors are designated *sarcoma osteoides*. As the cellular islands occupying the spaces between the spongioid trabeculæ of osteoid sarcoma are frequently well supplied with blood-vessels, they present the greatest similarity to cellular medullary spaces. Sometimes the osteoid substance presents a fibrous structure with long, delicate fibers, especially at the edges, and individual cells that have escaped from the general mass of the tumor-parenchyma are sometimes seen incorporated within the osteoid substance (Plate 58, Fig. 2).

When the osteoid substance undergoes secondary calcification, the first deposits of calcium usually take place

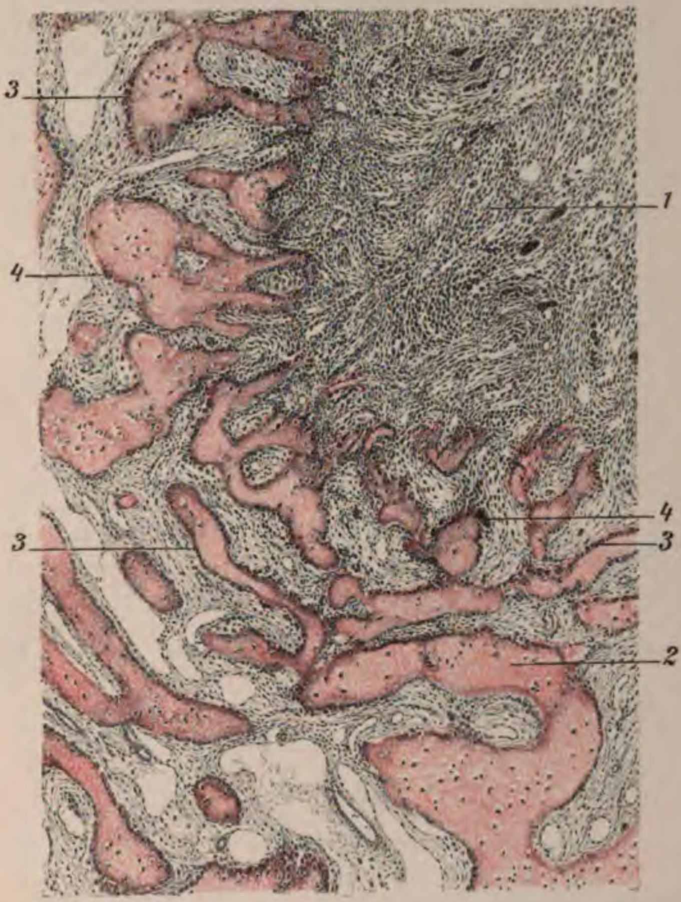


Fig. XXI.

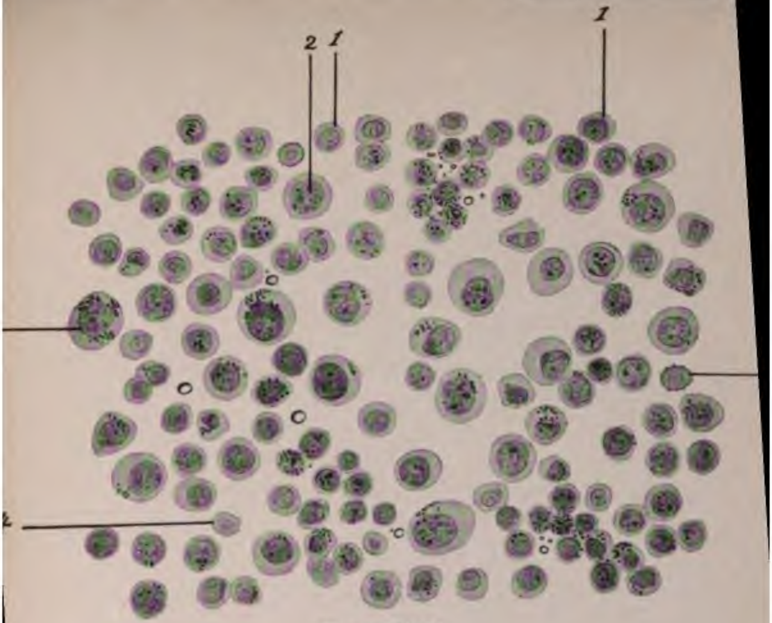
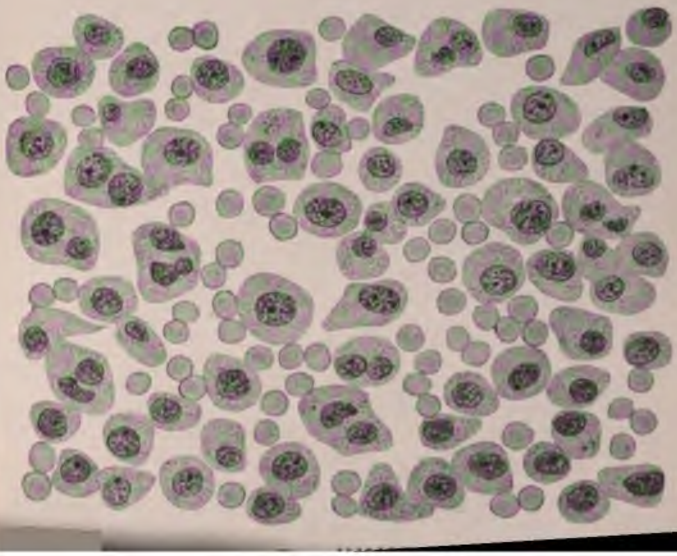


Fig. XXII.



around the cells, and from there spread further into the intercellular substance. The similarity to true bone-tissue thus becomes even more striking, although the lamellar arrangement is lacking.

The formation of true bone-substance is seen exclusively in those tumors which have their origin in the osteogenetic matrix of the skeleton itself. These represent a combined form, the true "osteosarcoma." Depending upon the seat from which the tumor springs, osteosarcomata are distinguished as *periosteal*, *myelogenous*, and *central*. They are characterized by the simultaneous production of a great variety of cells and a variable quantity of true bone, usually arranged like spongy bone.

Owing to the exceedingly destructive character of these tumors, the preëxisting bone is destroyed, and accordingly we here meet side by side the phenomena of bone-destruction and bone-formation, processes which usually follow a definite type, resembling the physiologic, and which are interesting in more respects than one.

If the new formation begins in the periosteum, the inner, so-called germinal layer, is almost always involved; the cells in this case consist chiefly of large spindle-cells with which giant-cells are associated in varying numbers. The growth takes place in two directions: outwardly, with the production of cellular masses and the apposition of bone-trabeculæ, and inwardly, toward the bone.

In the first zone are seen epithelioid groups, arranged in rows, proceeding from the proliferating cells; these secrete about them a calcifying, osseous ground-substance, and accordingly fulfil the functions of true osteoblasts. As in the case of physiologic osteogenesis, these epithelioid cells later become included in the lamellar systems that are formed and converted into bone-corpuscles with processes (Fig. XXI.). Absorption of the old bone is effected through the agency of giant-cells acting as osteoclasts, which cause a lacunar absorption—the formation of Howship's lacunæ; by cleavage of the bone-substance between the fibrils, producing von Recklinghaus
figures"; and, finally, by the forma

called perforating canals, vascular cords of sarcoma-cells growing into the bone-substance, and, so to speak, causing auger-holes in the substance. In this way the cortex is broken up gradually. The tumor penetrates the medullary cavity, where it continues to grow in exactly the same way as outside of the cortical lamella—*i. e.*, with the production of cells, which infiltrate the medullary cavity, and the new formation of bone-trabeculæ, at the same time that the original spongy constituents of the medullary cavity are removed. In the myelogenous osteosarcoma the order of growth is exactly the reverse. The cortex is destroyed from within, while on the outside of the bone a new cortical layer is produced in the form of a thin, parchment-like, continuous shell of bone. The latter often simulates a cortex distended by extensive growth; it has, however, nothing in common with the cortex, being formed long after the cortex itself has been destroyed by processes outside of the true tumor mass. As a rule, it does not sufficiently resist the destructive processes and later breaks down, and, with it, in the case of long bones, disappears; the last external barrier and the tumor-cells now spread outward without resistance.

The specific tumors of the skeletal system include the so-called multiple myeloma. This neoplasm originates in bone-marrow, and, to be more particular, exclusively from the red marrow of the ribs, vertebræ, or flat bones of the skull; it is noteworthy chiefly from the fact that it is almost always multiple, and appears in a number of bones at the same time. The marrow is converted into a soft, pulpy, grayish-red or dark-red mass. The spongy portion, as well as the cortical lamellæ of the affected parts of the skeleton, are absorbed, but the tumor almost never extends beyond the periosteum, and metastasis has not been observed. [Herrick and Hektoen have described a case with metastases in the ovaries.—Ed.] On microscopic examination large masses of round cells, presenting the character of lymphosarcoma or large, spheric, cells rich in protoplasm, and containing one or more often several vesicular nuclei, are usually found. Within quite recent times multiple myeloma has been regarded as a leukemic lymphoma. [A certain degree of albumosuria is characteristic of myeloma.—Ed.] The preparation shown in Fig. XXIII. is taken from a case of multiple myeloma of the ribs on the right side of the body, which developed after an injury. [Some of the cells in myeloma may resemble plasma-cells.—Ed.]

Melanosarcoma.—A sarcoma which has its origin in proliferation of pigmented connective-tissue cells is designated a melanotic sarcoma or melanosarcoma. As, however, pigmented connective-tissue cells are found exclusively in the skin and in the eye, the primary variety of these tumors occurs in these organs. By metastasis, however, they may appear anywhere in the body. Indeed, it may be said that melanosarcoma is the tumor which gives rise to the most wide-spread metastasis.

In the skin melanosarcoma starts most frequently in situations in which a tumor-like change with multiplication of the normal skin pigment is already present,—that is to say, in the so-called mother-marks, pigmented warts, *nevi.* It will, therefore, not be out of place to review once more the histology of pigmented nevi. As a rule, they consist of flat elevations; more rarely of small mushroom-shaped or polypoid tumors.

Throughout the entire nevus the epithelium is usually much attenuated in comparison with that of the surroundings. The stratum corneum is well preserved, and the cylindric basement cells are also usually demonstrable in every portion of the entire growth; but the rete Malpighii is extremely atrophic and reduced to only a few layers, the individual cells of which are low and imperfectly developed; while the intercellular bridges (spines and ridges) have disappeared altogether. The cause of this atrophy is discovered in the extraordinary elongation and lateral enlargement of the papillary body. The enlarged papillæ appear as broad cones of tissue with an extensive base, and they are exceedingly rich in cells. They push the epithelium before them, and, by distending it, cause its attenuation. The interpapillary epithelial

FIGURE XXIV.

Pigmented Nevus from the Skin of the Breast of a Newly Born Infant (× 65.): 1, Stratum corneum; 2, Malpighian layer, flattened by pressure; 3, epithelial plugs extending into the depths of the tissue; 4, pearls of horny epithelium; 5, non-pigmented masses of so-called nevus-cells; 6, nevus-cells containing an abundance of pigment; 7, papillary bodies.

plugs are also markedly involved. They are compressed laterally by the proliferated papillæ and often much increased in length, being drawn out into long, ridge-like, villous projections extending deeply into the corium. At the same time the interpapillary, horny layer is, of course, depressed into the depths of the tissue and covered here and there by the mucous layer, thus presenting veritable horny pearls (Fig. XXIV.), such as are observed in other proliferative processes which originate either in the epithelium or in the papillary body. Quite frequently the connection between the proliferating ridges and septa in the depths of the tissue and the surface epithelium is interrupted at certain points, so that in some sections masses of epithelial cells are found isolated in the deeper layers; although, if serial sections are made at some definite point, it is usually seen that these islands communicate with the superficial epithelium by cell-cords dipping down from the surface. The cells in the proliferated papillary body consist chiefly of spheroid and polygonal elements, exhibiting a variable amount of granular or fibrillar intercellular substance and compressed by the fibrous tissue into alveolar aggregations. The origin of these cells has been the subject of much lively discussion. Because an apparent connection is sometimes observed between the alveoli and epithelial ridges extending into the tissue, or with displaced epithelial islands, these cells, which, for the sake of brevity, we will simply call "nevus-cells," have been regarded by many authors (Unna and his school) as epithelial derivatives. Their shape, at all events, does not negative this view; but we have often seen that the shape of cells affords but little

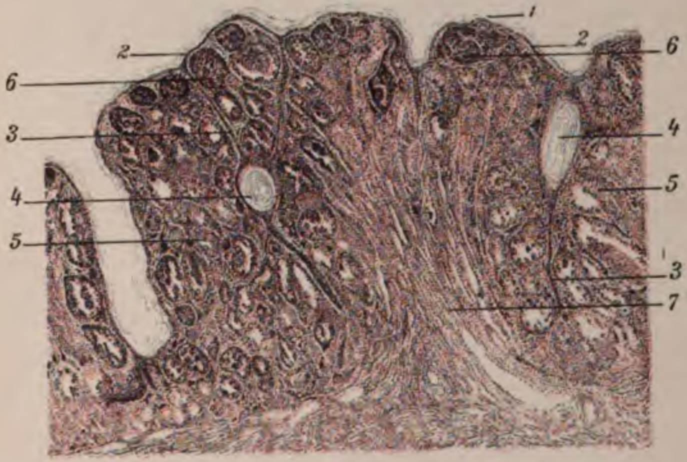


Fig. XXIV.

information about their origin and identity. Moreover, it is often possible in these tumors to demonstrate at the edges of the alveoli a direct connection of the large cells contained in them with surrounding fibers and with delicate, spindle-shaped, connective-tissue cells, thus indicating that the large cells [nevus-cells.—ED.] belong to cells of the corium. Down toward the tissue of the cutis a direct transition of the contents of the alveoli into dense, diffuse, cellular accumulation at the deepest portion of the enlarged papillæ is not infrequently observed. The nevus-cells, although arranged in alveoli, are to be regarded as connective-tissue cells. It may be mentioned that many authors believe they originate in endothelial elements of the blood- or lymph-vessels.

Pigment may be present in variable quantities in all the constituents of the nevus. Almost always the attenuated and atrophic epithelium shows deeper pigmentation than the surrounding tissue; the cells of the cylindric basement layer especially are usually overloaded with brown pigment-granules, much as in Addison's disease (compare Plate 20, Fig. 2). The true nevus-cells, however, are the chief deposits of pigment, but the distribution is extremely irregular. While some alveoli contain nothing but darkly pigmented cells, others in immediate apposition may be entirely free from pigment, or the same alveolus may contain, in addition to a few absolutely brown or almost black cells, a preponderating number of unpigmented cells. The local distribution of the pigment is also quite variable, it being sometimes more abundant in the upper and sometimes in the deeper layers. In addition, pigment is almost always found scattered throughout the stroma, where it is usually imbedded in spindle-shaped or stellate connective-tissue cells, such as are seen normally in cases of deep pigmentation of the skin and are known as *chromatophores*. These cells can be traced far down among the dense connective-tissue fibers of the subjacent tissue (compare Plate 21, Fig. 2, under Pigment).

With slight deviations the *cutaneous melanosarcoma*, at least in its initial stages, exhibits practically the same pic-

PLATE 60.

FIG. 1.—**Melanosarcoma of the Skin** (Hemat.-eosin. × 42.): 1, Epidermis with somewhat flattened papillary body; 2, thickened cutis; 3, strands of intensely pigmented, stellate cells (chromatophores).

FIG. 2.—**Melanosarcoma of the Choroid** (Hemat.-eosin. × 300.): 1, Spindle-cells; 2, vascular spaces; 3, intensely pigmented spindle-cells.

PLATE 61.

FIG. 1.—**Freshly Isolated Cells from a Metastatic Melanosarcoma of the Peritoneum.** (Dark Masses of Pigment of Varying Sizes. × 280.)

FIG. 2.—**Cells from a Metastatic Melanosarcoma of Bone-marrow** (Freshly Isolated. × 280.)—Distinct chromatophore character.

FIG. 3.—**Freshly Isolated Glomeruli from the Kidney in Universal Melanosarcomatosis** (× 280.).—The greater portion of the vascular loops filled with melanotic pigment.

FIG. 4.—**Metastatic Melanosarcoma of the Peritoneum** (Hemat.-eosin. × 320.): 1, Nests of darkly pigmented polygonal cells; 2, cross-section of vessels.

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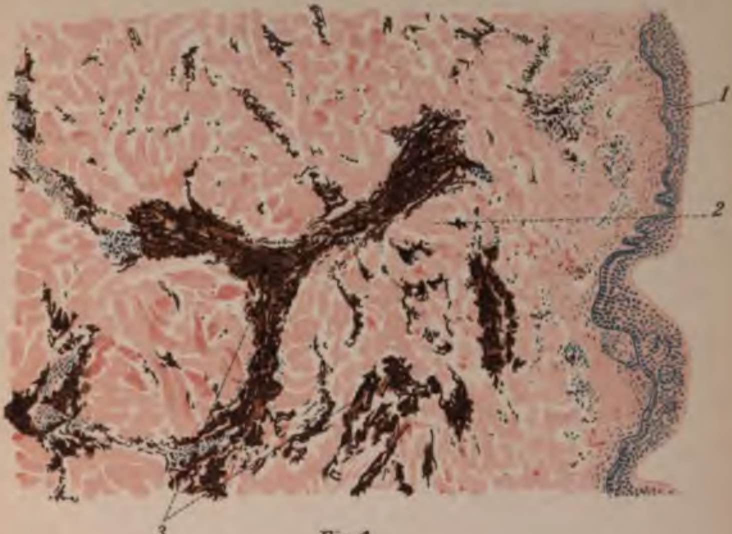
tures. The true tumor-parenchyma consists of polymorphous cells which closely resemble the above-described "nevus-cells," not only in appearance, but also as regards their position and arrangement. They consist of large spindle-cells with a few spheroid and polygonal elements; occasional giant-cells may also be scattered among them. The pigmentation in the tumor is also extremely irregular and distributed in patches.

At first the pigment is exclusively intracellular, in the form of exceedingly minute, dust-like granules, or larger, round or irregular clumps. The color varies from bright yellowish-green to the darkest shade of brownish black. The cells may be so heavily loaded that the pigment obscures both the protoplasm and the nucleus, or only a few scattered particles may be deposited in a cell, or the nucleus at first appears to escape and pigment-granules occupy the periphery of the cell in the form of a wreath. Sometimes irregular branching strands or linear and

Tab. 60.



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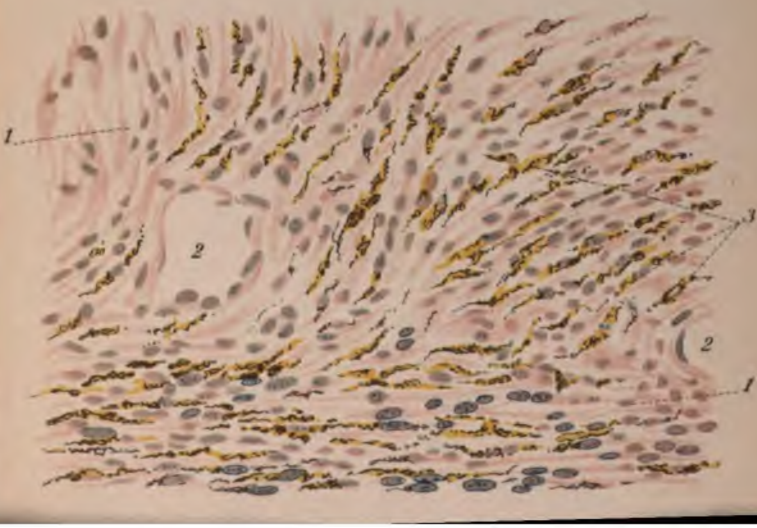


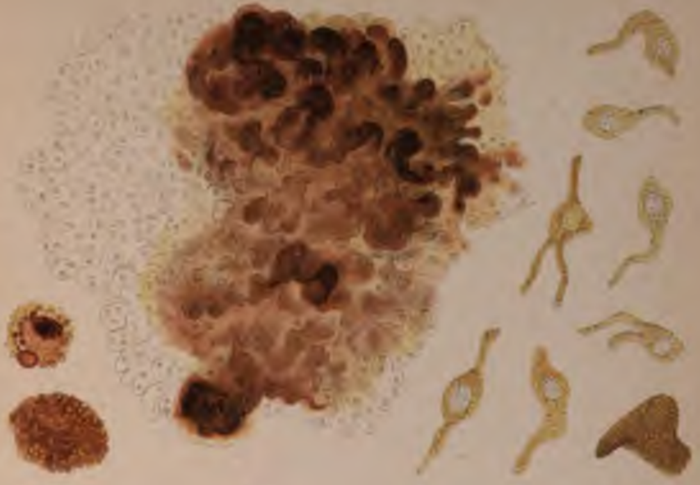
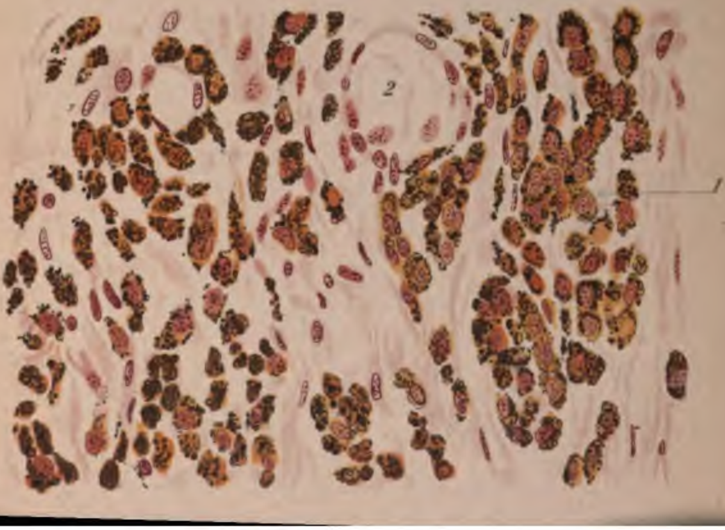


Fig. 1. Fig. 3. Fig. 2.



spindle-shaped accumulations of pigmented cells are found at some distance from larger aggregations of pigmented cells in the corium and in the cutis (Plate 60, Fig. 1). The smaller of these accumulations give the impression of being lymph-clefts filled with pigment-cells, and it is possible that the larger strands have been produced in the same way, with secondary dilatation of the lymph-channels and infiltration of their walls with pigmented tumor-cells. Certain relations with the blood-vessels may also be discernible, some of the smaller arterial or venous branches, or sometimes capillaries, being completely enveloped by a cylindric mantle composed of pigment-containing cells. Wherever the cells are more isolated, they exhibit a stellate shape or they may be ovoidal, provided with several branching processes, which occasionally form extremely delicate structures that exhibit the greatest resemblance to so-called chromatophore figures (Plate 60, Fig. 2; Plate 61, Fig. 3). Owing to the similarity of the tumor-cells to epithelial cells, already referred to in connection with pigmented nevi, and their "epithelioid" grouping, these tumors were formerly thought to be derived from pigmented cutaneous epithelium and accordingly were designated *melano-carcinoma;* but in this case also intercellular substance and connection with the surrounding stroma can frequently be demonstrated.

The melanotic sarcoma of the eyeball grows from the pigmentary layer of the choroid. Here again, as in the case of the pigment-containing basal layer of the epiderm, the pigmented epithelium of the retina always escapes. Usually the tumor manifests itself as a spindle-cell sarcoma (Plate 60, Fig. 2). The individual cells are fairly large structures, rich in protoplasm, frequently presenting a typical perivascular arrangement, often immediately contiguous with the endothelium of the vascular tubes. Here again the pigmentation is usually not uniform. Side by side with cells entirely void of pigment others are found in which the cellular shape can be recognized only by the outlines of the pigment-masses:

the nuclei also may be completely obscured by the abundance of pigmentary deposit, or the granules may be more concentrated at the two poles of the spindles, while the nuclear center of the cell-body contains but few pigment-granules or none at all. The color of the pigment-granules is usually yellowish brown; much less frequently dark brown, like that in the skin. Sometimes branching, stellate elements are found along with the spindle-shaped cells, and by their shape suggest normal chromatophores. Transverse sections of the spindles may simulate round-cells.

The enormous metastatic distribution of pigmentary sarcoma in the body is a well-known phenomenon. There is hardly an organ in the body that may not be attacked by this metastasis, and sometimes the distribution may be so universal as to compel the conclusion that there has been a complete inundation with tumor-cells. Here again the distribution of the pigment is most variable and remarkable. Sometimes the pigment is disseminated as such in the body, and is deposited in the intima of the blood-vessels, where it produces circumscribed brownish macules or a diffuse discoloration; or the pigment may be deposited in large masses in the kidneys, so that the epithelium of the convoluted and straight uriniferous tubules becomes diffusely infiltrated (see *Atlas of Special Pathologic Histology*, Vol. II., Plate 80). In such cases it also appears in the urine (melanuria), and causes a dirty, brownish-gray discoloration of this fluid. The glomeruli sometimes appear to be densely packed with pigment, and the individual vascular loops are stuffed full of pigment-thrombi in the form of dark-brown, sausage-shaped bodies. Bowman's capsules are also similarly filled.

Quite frequently the spleen and bone-marrow are flooded with metastatic pigment or occupied by tumor-masses. In the metastatic growths the original character of the tumor-cells is often quite well preserved. Thus Fig. 2 in Plate 61 represents isolated cells from metastatic growths in the bone-marrow, in which chromatophores with processes are distinctly visible.

Chloroma is a tumor which belongs to the same family as melanosarcoma. It usually grows from the periosteum (cranial bones, ribs, vertebra) (Risel) or from the bone-marrow, and is distinguished by a characteristic green pigmentation of its parenchyma. The pigmentation is most distinct in perfectly fresh specimens, and gradually fades on exposure to the air, usually disappearing altogether in preserved specimens. The tumor consists, in the main, of mononuclear, usually spheroid, cells, after the type of lymphocytes; sometimes multinuclear round-cells and cells with a greater abundance of protoplasm occur. On account of this structural peculiarity the neoplasm has been compared to lymphosarcoma (Von Recklinghausen). The mode of origin of the pigment is not clear; while a good many authors regard it as a parenchymatous pigment, others explain it as altered blood-pigment on the ground that this form of tumor is frequently observed in association with diseases of the blood and of the blood-forming apparatus, with diminution in the number of red blood-cells and in the percentage of hemoglobin. [Dock in particular has studied its relations to leukemia.—Ed.]

EPITHELIAL NEOPLASMS.

The term epithelial neoplasms is applied to tumors the histologic character of which is materially influenced by the participation of epithelial tissue in the proliferation. Since, however, simple epithelium is always a perishable formation requiring for its existence a certain quantity of supportive substance, and for its nutrition a certain proportion of blood-vessels, it is evident that a purely epithelial tumor—that is, one composed exclusively of newly formed epithelium—is an impossibility, and, accordingly, when we speak of an epithelial neoplasm, we necessarily mean a combination of epithelium and a variable quantity of vascular connective tissue. A well-marked stroma is present, which contrasts sharply with the tumor-parenchyma formed from the proliferation of epithelium; hence these tumors, on account of their resemblance to organs composed of different tissues, have been called *organoid tumors*, in contradistinction to the histoid tumors, which consist of a single kind of tissue. But it has already been pointed out, in the discussion of connective-tissue tumors, that this distinction cannot always be strictly observed. For in many kinds of sarcoma the simultaneous development of a true proliferating tumor-mass and of a supportive tissue is quite evident, and the distinction between the parenchyma and the stroma is the more evident the greater the differentiation of the actual tumor-tissue from the character of simple, fibrous connective tissue. But this division into tumor-parenchyma and stroma in the case of connective-tissue tumors is justified solely by the morphologic facts. The cells of the so-called tumor-parenchyma, it is true, present but little similarity to genuine connective-tissue cells; but, so far as their origin is concerned, they, nevertheless, represent derivatives of the mesenchyma just like the elements of the stroma. In the epithelial tumors, on the other hand, the division into tumor-parenchyma and stroma is justifiable on genetic grounds, for the former is always contributed by germs that are not derived from the mesenchyma.

The distribution of connective and epithelial tissue is without uniformity or regularity. When the two components take an equal part in the building-up of the tumor, as in the histologic structure of normal organs, and the development of the tumor therefore depends materially upon connective-tissue growth, a so-called fibro-epithelial tumor results which in its structure reproduces normal components of the body. Epithelium and connective tissue in these tumors preserve the intimate contact which enables them to take part in the building-up of organs. On the other hand, the epithelium may proliferate quite independently of the connective tissue, and thus set its mark upon the neoplasm by penetrating in an irregular and atypical manner into the surrounding tissue. It is obvious that, for its continued existence, the epithelium requires a certain amount of vascular supportive substance; in fact, the development of the latter may be quite well marked; the character of the tumor, however, is not determined by the quantity of epithelial or connective tissue that takes part in its formation, but by the relation of the former to its surroundings, as compared with normal epithelial structures. Those histoid tumors, in which the epithelium, accompanied by a variable quantity of connective tissue, invades the neighboring tissues in a destructive manner and presents an atypical character in its spatial relations to other tissues, are known as carcinomata.

Fibro-epithelial Tumors.

Fibro-epithelial tumors may take their origin either from the skin and mucous membranes or from glandular structures. In both cases combination tumors result which present either a papillary structure, and are then designated *papillomata* or *papillary epitheliomata*, or they may manifest a glandular structure and represent *adenomata*. In adenoma, especially in the dilated cystic cavities which

PLATE 62.

FIG. 1.—**Tubular Adenoma of the Mamma** (Hemat.-eosin. × 80.): 1, Cellular connective tissue; 2, tubules, some with several layers of cells in their lining.

FIG. 2.—**Adenoma Tubulare Fibromatosum of the Mamma** (Hemat-eosin. × 80.): 1, Celular connective tissue; 2, compressed gland tubulæ, some of them invaginated.

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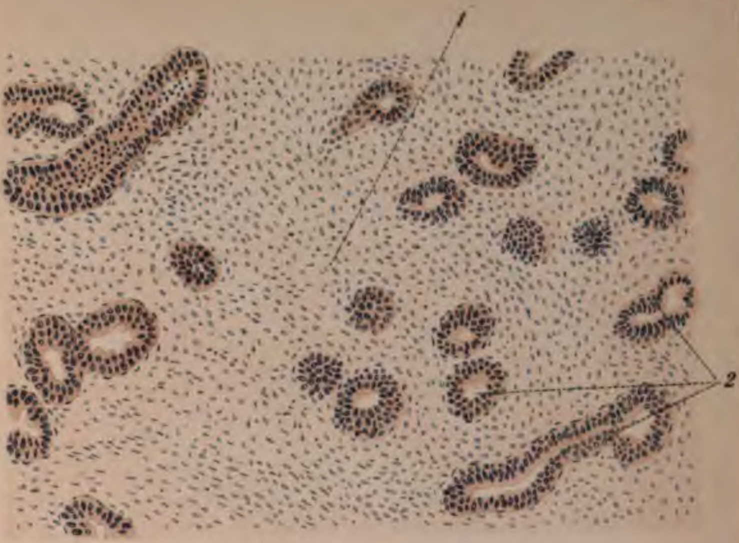
such tumors contain, papillary elevations of connective tissue may form secondarily and push the epithelium before them, invaginating the same into the lumen of the cavities and thus producing a so-called papillary adenoma.

Papillary Epithelioma.—The papillary epithelioma, or papilloma, derives its origin from primary proliferation of the papillary body or of the submucous tissue. It is not to be denied that in many tumors belonging to this category the epithelial tissue is so much in excess that it appears to play a primary part in the growth of the neoplasm; but more careful investigation will show in every case, even when the accumulation of epithelium is most voluminous, a central framework of connective-tissue substance presenting certain definite changes, so that it must be concluded that this connective tissue unquestionably takes the initiative in the formation of the tumor. In the simplest case a mere plug of connective tissue is formed, the true papillary body being absent, or, if the papillæ are present, they become elongated. The papillæ may grow out to an extraordinary length, and otherwise present many variations from the normal, being often exceedingly broad or branching, or possessing a club-shaped enlargement at their apex; or they may be of a spiral shape and anastomose with one another.

In every case these abnormal papillary formations contain blood-vessels; these often attain an extraordinary development, and form a veritable network which throws the accompanying connective tissue completely into the background (Plate 63, Fig. 1). This explains why many tumors belonging to this category possess an extraordinary tendency to hemorrhage, which is often quite severe, as,



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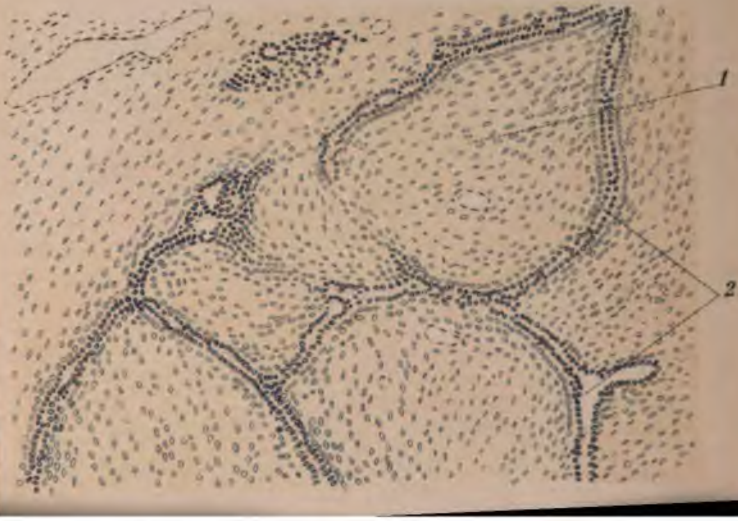

for example, in papilloma of the urinary bladder. The epithelium is pushed up by the papilloma and stimulated to superficial enlargement because it is forced to follow all the ramifications, elongations, and lateral enlargements of the underlying tissue. But it may itself exhibit many variations in its development—from a simple investment, consisting of a single layer of cells, to structures composed of innumerable layers, completely filling the interspaces between adjoining papillæ or their branches, and this in spite of many clefts in the papillary body, thus giving the surface an approximately smooth appearance. In the latter case the layers of epithelium must, of course, be greatly multiplied as compared with normal conditions. In sections the histologic picture often simulates an active villous encroachment of the epithelium on the underlying connective tissue; but when the normal level of the base is determined, it is found in almost every case that the epithelium in its downward growth has not overstepped the physiologic limit, or at most only to a very insignificant extent.

The most frequent site for the development of these papillary epitheliomata is the skin, where these structures are designated *warts* or *verrucæ*. The common peculiarity of these tumors is a local hyperplasia of the papillary body, which may attain a variable degree. It may either represent elevations in the form of a truncated cone with broad, sessile base, covered with epidermis, which is little altered or merely thickened, and thus producing flat or spheric warts; or the papillary body may be extraordinarily enlarged and exhibit slender processes which often branch at the ends; the spaces between these processes are filled with epithelium or bridged by epithelial cells (Plate 66, Fig. 2). If the epithelium occupies the entire extent of the long-drawn-out papilla from the base to the surface, it is evident that the layers must be greatly multiplied. This results in numerous depressions, wrinkles, and cleft-formations in the epithelial tissue, and as the individual layers generally retain their histologic character, concentrically laminated masses are thus produced in the depth of the tissue, which from within outward present the same structure as normal epidermis from above downward. In this way pearl-like bodies may be produced in which an extraordinary development of the corneal layer is discernible. The latter appear in the form of pale, concentrically striated spheric masses, which, as the result of the marked invagination, may often be found as far down as the base of the papillary body. As the branching of the papillary body, of course, occupies every plane in space, a microscopic section will often show circular cross-sections of vascular papillæ that appear to be surrounded on all sides by epithelium (Plate 56, Figs. 2 and 3).

Occasionally the thick epithelial layers, especially the desiccated superficial horny layers, are broken up by numerous fissures; any slight traumatic influence may also cause a laceration of the deeper layers and of the papillary body, followed by the invasion of inflammogenic organisms. In this way inflammatory phenomena may appear secondarily in the proliferated papillary body; in fact, a wart may undergo actual suppuration and the epithelial layers become infiltrated with masses of leukocytes. Sometimes the participation of the individual layers of epithelium is unequal. Above a more or less distinctly marked basement-layer there may be an enormous multiplication of the stratum spinosum—the prickle-cells and ridge-cells of the Malpighian layer (*acanthoma*). These cells swell up until they form very large, pale structures. Sometimes drops of fluid collect in vacuoles within the cells and force the nucleus toward the cell-wall, where it assumes a crescentic shape. The stratum corneum is sometimes sparingly developed, while in other cases an extraordinary development takes place. Thus, the rete Malpighii may be very low and the horny layer spread out over it in the form of numerous wavy layers, reproducing the shape of the substratum. In this way an enormous local hyperplasia of the horny substance may be produced (*ichthyotic skin warts*), which may often be congenital (Ziegler) [*ichthyosis*.—Ed.]; or true horny appendages of the skin are formed in which the horny substance may attain the thickness of several centimeters (*cutaneous horn*). Histologic examination with Gram's method usually shows the abrupt appearance of keratin globules in the rete Malpighii and simultaneous cornification of the superincumbent layers. Sometimes the papillary body in these cutaneous horns is extraordinarily long, suggesting that these structures also have their origin primarily in proliferation of the connective tissue of the skin.

In many cases primary inflammatory changes in the corium and in the cutis are discoverable at the site of a papillary epithelioma. An example of this is found in the so-called *acuminated condyloma*, which occurs preferably in chronic catarrh of the urethra, vagina, or rectum, at the boundary between the mucous membrane of these organs and the external skin (Plate 67, Figs. 1, 2). The papillary body often exhibits small-cell infiltration. In the connective tissue embryonal forms of cells are frequently seen; the vessels are dilated, and often contain numerous leukocytes. The enormous hypoplasia of the epidermis which is observed in these formations chiefly affects the rete Malpighii, while the horny layer, as a rule, is only sparingly developed. Sometimes the epithelium contains accumulations of leukocytes, or the cells are in part swollen as the result of the abundant infiltration with serous exudate, or they may be forced apart.

In the mucous membrane the so-called soft, papillary epitheliomata are more frequent, and, here again, the boundary-line between true autonomous tumors and secondary formations on a chronic inflammatory base is difficult to determine, as the latter often cause a local hyperplasia of the connective tissue of the mucous membrane with secondary bulging of the epithelium. In this way the well-known polypoid structures are formed in the nose (Plate 43), which have already been discussed in connection with fibroma. In these tumors also proliferation of the epithelium may sometimes take place, especially proliferation of the glandular epithelium, which is elevated along with the surface epithelium. This proliferation of tissue takes the form of deep, sinuous depressions or variously convoluted tubular structures; in other words, they also present a superficial enlargement, often combined with an unusually abundant production of goblet-cells. The stroma of these tumors is generally soft and succulent, the fibers are forced apart by edematous fluid, and the intercellular substance often exhibits true mucoid change, demonstrable with acetic acid, while the connective-tissue cells present the well-known stellate structure of myxomatous tissue (Fig. XI.). The stroma contains an abundance of leukocytes and often numerous round-cells of the character of eosinophile cells. In the larynx and in the trachea, as well as in the gastro-intestinal canal, excrescences may be produced in this way which are due to the local proliferation of the connective tissue in the mucous membrane and are accompanied by multiplication and superficial enlargement of the overlying epithelium, as well as of the glandular portions that have become involved in the morbid process.

Papillary epitheliomata of characteristic structure occur in the urinary bladder. They usually possess an exceedingly delicate, branching stroma, traversed by very thin-walled blood-vessels. This stroma is everywhere clothed with stratified epithelium, which, as regards the shape of its cells, corresponds to the lower and intermediate layers of the vesical mucous membrane (so-called *villous papilloma of the bladder*), and may occasionally exhibit at the apices of the papillæ long-drawn-out, spindle-shaped cells. Frequently a partial separation of individual portions of these villous formations takes place during life, and, owing to the great abundance of blood-vessels, this may be followed by severe hemorrhage. Sometimes, as a result of torsion of the pedicle of individual villi, parts of the tumor may undergo necrosis and are then usually rapidly covered with an incrustation of urates. Villous epithelioma also occurs in the upper portions of the urinary passages, the ureters, and the pelvis of the kidney, as well as occasionally in the uterus. In the gall-bladder and in the large bile-ducts the mucous membrane is sometimes covered with small, wart-like elevations, consisting of a delicate connective-tissue framework and a thin covering of epithelium (*cholecystitis polyposa*).

Adenoma.—Adenomatous structures are also the result of a combination of connective and epithelial tissue. In order that the tumor-like character be preserved, a uniform participation of the two tissues as regards distribution is necessary; but the origin of these tumors, however, in every case seems to be referable to the primary proliferation of the epithelial tissue. As it multiples the latter dips down into the clefts of the surrounding connective tissue, where it is at once joined by a certain quantity of connective tissue, which adapts itself closely to the newly formed epithelial layer. In fact, it has been thought by some authors (Borst) that the epithelium possesses a so-called tactile sensibility. Adenoma always originates in glandular organs, particulary in the large parenchymatous organs, the mammary glands, the kidneys, the ovaries, the liver, the testicles, or in the mucous glands of the gastro-intestinal canal, the uterus, and the respiratory tract, and finally in the skin-glands. Here also the degree to which the connective tissue takes part in the process is extremely variable both qualitatively and quantitatively. It may be so much in excess of the newly formed epithelial constituents that the term primary fibroma has been used. On the other hand, its development may be scanty as compared with the abundant formation of gland-spaces. In every case, however, all the epithelial parts of the adenoma are surrounded by a continuous layer of connective tissue. It is often possible to demonstrate a true tunica propria, supporting the epithelial cells exactly like the normal glandular structures. Occasionally the stroma is firm and fibrous, containing only a few small spindle-cells, while the fibers in places are so closely packed as to form a sclerotic and often hyaline mass; again, adenoma is sometimes observed with a cellular, delicate, reticular stroma, in the meshes of which numerous wandering cells, especially eosinophile cells, may be demonstrated, while the fixed cells of the

FIGURE XXV.

Pericanalicular Adenoma of the Mamma (× 80.): 1, Compressed gland-tubules; 2, segments of such tubules; 3, concentrically striated connective tissue arranged around the canaliculi; 4, blood-vessel.

FIGURE XXVI.

Intracanalicular Adenoma of the Mammary Gland (× 280.): 1, Gland-tubule invaginated by proliferating connective tissue (3); 2, reflection of the epithelium; 4, eosinophile cells in the connective tissue.

PLATE 63.

Fig. 1.—**From a Papillary Cystadenoma of the Ovary—Cross-section of a Papilla** (Hemat.-eosin. × 220.): 1, Epithelial covering; 2, connective tissue; 3, injected vessels.

Fig. 2.—**From a Papillary Cystadenoma of the Ovary** (Hemat.-eosin × 80.): 1, Connective tissue; 2, lumen of cyst; 3, connective-tissue papilla pushing the epithelium before it (4); 5, sections of papillary excrescences.

Fig. 3.—**Papillary Cystadenoma of the Ovary** (Hemat.-eosin. × 150.): 1, Connective-tissue stroma; 2, epithelial covering, consisting of many layers; 3, papillary excrescences with elevation of the epithelium; 4, epithelial wrinkling.

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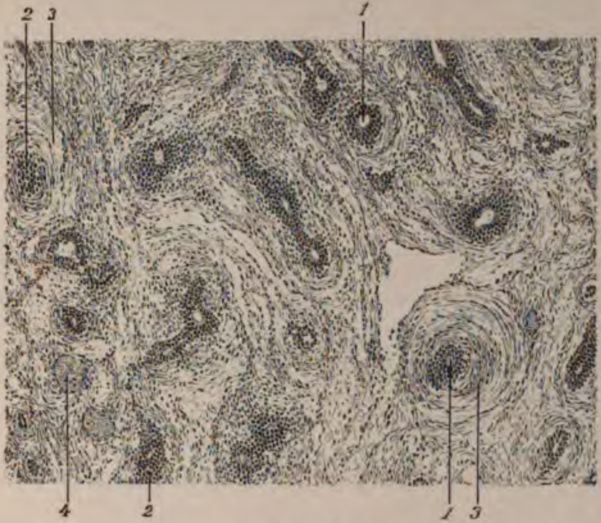
tumor consist of large spindle-shaped or stellate elements with an abundance of protoplasm. The interstitial tissue may become swollen from the accumulation of edematous fluid, or the ground-substance may undergo metaplasia resulting in true myxomatous degeneration (*adenomyxoma, adenofibroma myxomatodes*).

Depending upon the development and character of the epithelial portion it is usual to distinguish *tubular*, *alveolar*, and *follicular* adenoma. In the first group the epithelial neoplasms imitate the excretory ducts of glands and represent tubular structures the epithelial lining of which usually consists of a single layer of cells, rarely of more. The individual cells may be cuboidal, cylindric, or sometimes flat. Oblique sections of such tubules often simulate stratified structures which appear to anastomose



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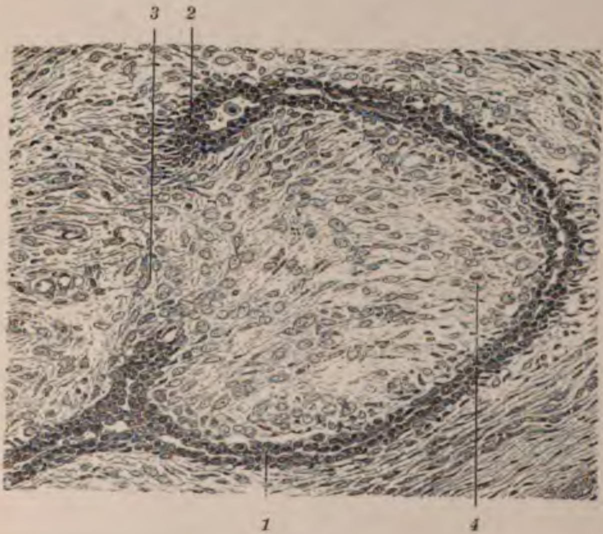

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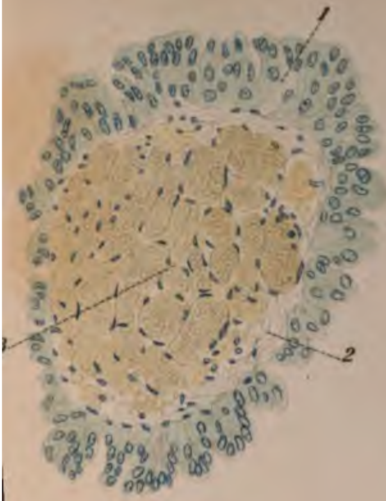

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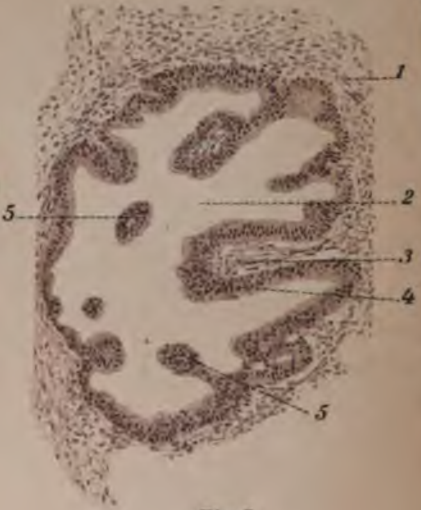

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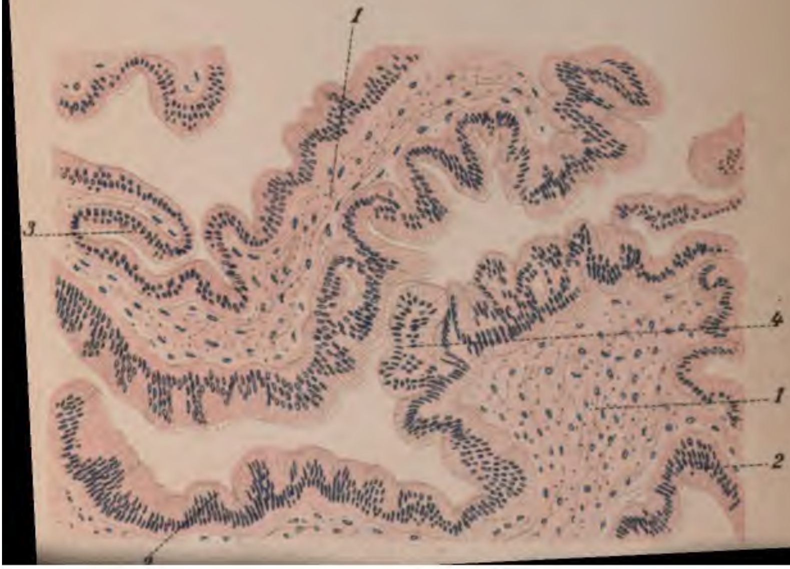

with one another. They may also send out into the interstitial tissue sprouting processes, sometimes with dilated extremities. Occasionally a distinct secretion is found in the glandular neoplasms, in that large quantities of mucin, pseudomucin, or colloid substance are produced, or in liver-adenoma, bile. These secretory processes, however, quite frequently possess a distinctly degenerative character and lead to the death of the secreting cells. In fact, one may actually speak of mucoid or colloid degeneration of the adenoma-cells. When the growth of interstitial connective tissue is particularly marked, it sometimes gives the adenoma a special morphologic character, as the connective tissue often assumes an aggressive stand toward the newly formed gland-spaces. Either it constricts the glandular canals with closely packed fibrous rings until the glandular lumen is completely obliterated (*adenoma pericanaliculare*) or it advances actively against the newly formed epithelial cells, causing an invagination of the glandular spaces like the fingers of a glove and the apposition of the epithelium so as to form several layers (*adenoma intracanaliculare*) (Figs. XXV. and XXVI.). The latter phenomenon is apt to take place particularly after cystic dilatations or clefts have been previously produced within the gland-spaces. The connective tissue then dips down in the form of blunt papillæ with club-shaped enlargements at their extremity, or in the form of a rolled-up leaf, and comes against the wall of the epithelial spheres and cylinders, pushing the epithelium in front of it, as in the formation of a papillary epithelioma. As the connective tissue in most of these cases is extremely cellular, they have been described as cases with simultaneous sarcomatous growth, and those tumors, which have their seat chiefly in the mammary gland, were formerly often designated *adenocystosarcoma*, with the addition of the epithet "phyllodes," in view of the leaf-like invaginations.

Adenoma also frequently exhibits certain similarities to chronic inflammatory processes, and in many cases they are difficult to differentiate from simple inflammatory

PLATE 64.

FIG. 1.—**Papillary Adenoma from the Rectum** (Hemat.-eosin. × 98.): 1, Vascular stroma; 2, stratified cylindric epithelium.

FIG. 2.—**Polypoid Adenoma from the Rectum** (Hemat.-eosin. × 42.): 1, Tubular gland-spaces, with manifold epithelial wrinkling and epithelial bridges; 2, large cystic gland-spaces; 3, connective-tissue stroma.

PLATE 65.

FIG. 1.—**Multilocular Glandular Cystoma of the Ovary** (Hemat.-eosin. × 35.): 1, Cystic gland-spaces; 2, folds of epithelium; 3, stroma.

FIG. 2.—**Papillary Cystoma of the Ovary** (Hemat.-eosin. × 80.): 1, Gland-spaces; 2, same, with numerous epithelial folds; 3, epithelial fold in horizontal section; 4, stroma.

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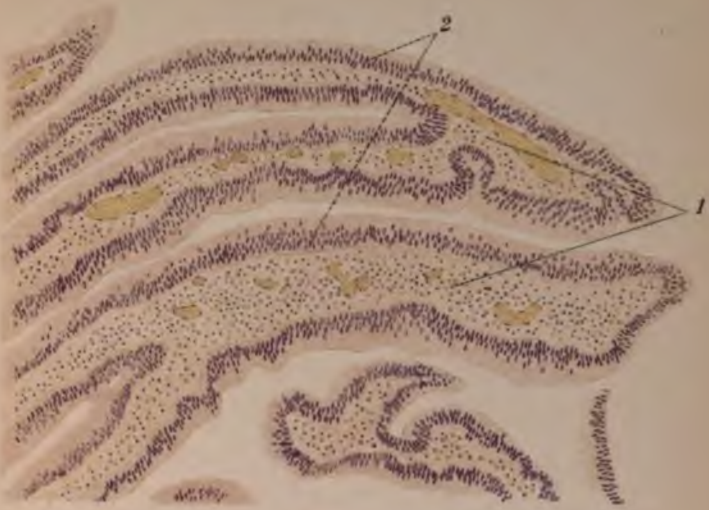
hyperplasia. This is especially the case in the adenomatous neoplasms of the nose, the uterus, and the gastro-intestinal canal. Polypoid growths of the nasal mucous membrane often contain such an abundance of proliferating gland-tubules that the stroma is completely overshadowed, and the entire tumor appears to consist of interlacing glands. As a rule, the chronic catarrhal conditions which are the cause of their formation are still demonstrable. There is increased secretion, with the formation of numerous goblet-cells and a continuous procession of leukocytes through the epithelium. In the so-called glandular polypi of the stomach and intestines these chronic inflammatory conditions in the connective tissue and catarrhal processes in the epithelial portion are clearly discernible. In the stomach particularly hyperplasia of the interstitial tissue occurs on a base of chronic catarrh, and leads to multiple, polypoid bulgings of the mucous membrane and simultaneous multiplication of the epithelial cells of the gastric glands. In this way may be produced either multiple polypoid adenoma, extending over large portions of the mucous membrane, or solitary neoplasms as large as a goose-egg, their surface interrupted by numerous fissures and consisting almost exclusively of



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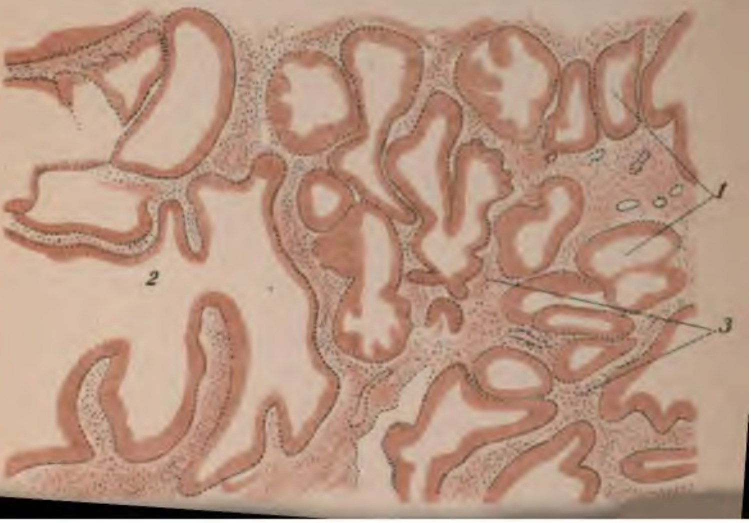

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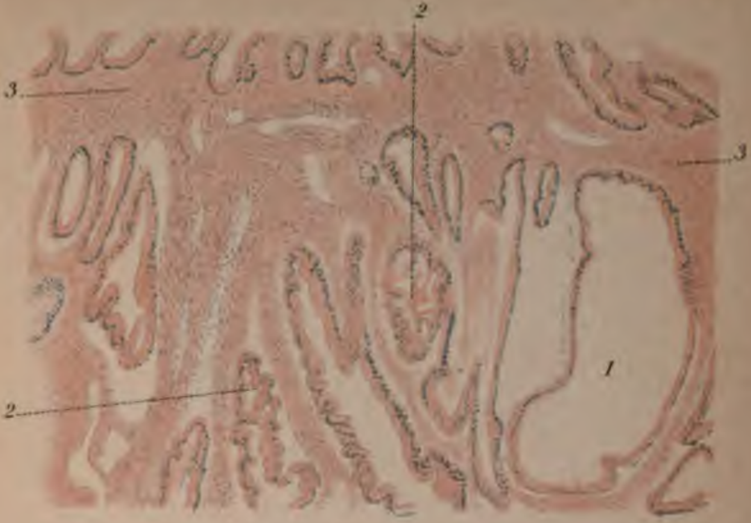

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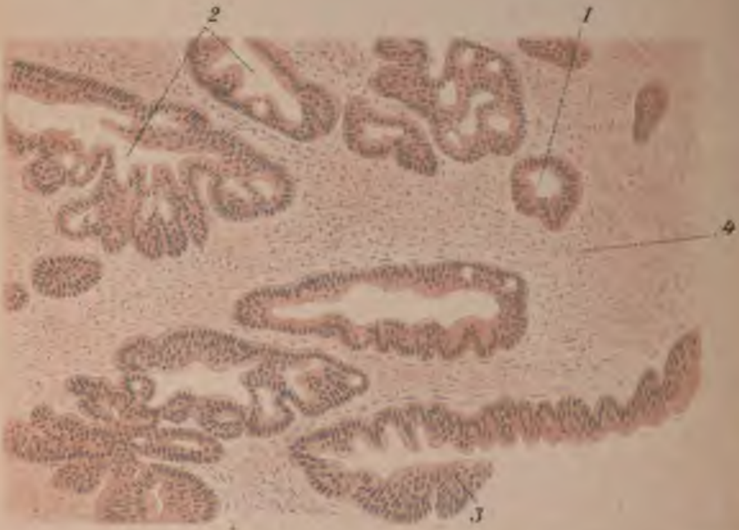

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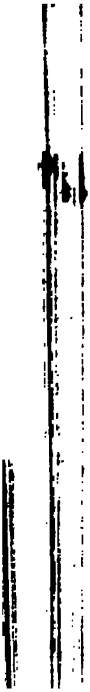

degenerated glands and a scanty amount of interstitial tissue. Quite similar structures are occasionally found in the large intestine, especially in the rectum, where broad, sessile, polypoid hyperplasiæ of the connective tissue of the mucous membrane, thickly covered with corkscrew-like spiral glands, are often produced (Plate 64, Fig. 2).

Cystoma.—When dilatation of the cavities in an adenomatous tumor takes place, the structure is known as a *cystoma* or *cystadenoma*. The dilatation cannot well be attributed exclusively to the pressure of the increased secretion from the epithelium, because, if that were the case, atrophy would soon make its appearance in the latter; it seems more probable that the surface of the epithelium itself becomes enlarged and is partly responsible for the great increase in size. In these tumors also the epithelial covering usually consists of one layer, but oblique or horizontal sections through the domes of smaller cysts may simulate a covering of several layers or even solid alveoli filled with epithelium. The superficial growth of epithelial cells is often pronounced, and manifests itself not only in the enlargement of the cystic spaces, but also in the formation of numerous folds, which either project into the external surrounding connective tissue, where they at once form a lumen and lead to the production of daughter-cysts (Plate 65, Fig. 2), or follow the line of least resistance and grow toward the interior of the tumor, forming an invagination which is often irregularly branched and projects into the lumen. In addition, the epithelium may also be pushed toward the interior of the tumor by active growth of the subepithelial connective tissue, thus forming the papillary structures which are so frequently found on the inner surface of cystic cavities at times filling the anterior. They evidently consist of a combination of cystic formation with secondary papillary elevations toward the lumen (*papillary cystoma*). These epithelial invaginations always possess a central stalk of vascular connective tissue, which does not always become evident in superficial sections of the papillæ, and becomes apparent

PLATE 66.

Fig. 1.—**Atypical Proliferation of Epithelium from the Edge of an Ulcer of the Leg** (Hemat.-eosin. × 70.): 1, Stratum corneum; 2, stratum Malpighii; 3, tall, broad, connective-tissue papillæ; 4, plugs of epithelium, proliferating into the depth of the tissue; 5, epithelial islands entirely surrounded by connective tissue and without any apparent connection with the superficial epithelium.

Fig. 2.—**Papillary Epithelioma of the Skin with Pearls of Horny Epithelium (Horny Wart)** (Hemat.-eosin. × 20.): 1, Normal epiderm; 2, thickened tissue in the cutis; 3, transverse section of tall and branching papillæ; 4, concentrically striated horny masses.

PLATE 67.

Fig. 1.—**Papillary Epithelioma (Condyloma Acuminatum from Labium Majus)** (Hemat.-eosin. × 20.): 1, Tall branching connective-tissue papillæ; 2, transverse section of connective-tissue papillæ within the epithelium; 3, thickened layers of epithelium; 4, blood-vessels.

Fig. 2.—**From a Papillary Epithelioma of the Labium Majus (Condyloma Acuminatum)** (Carmin. × 80.): 1, Papillæ in longitudinal section; 2, transverse sections of papillæ with distended blood-vessels; 3, thickened layer of the rete Malpighii; 4, cylindric germinal cell-layer of the epiderm.

PLATE 68.

Fig. 1.—**Papillary Epithelioma from the Bladder (Villous Papilloma)** (Hemat.-eosin. × 35.): 1, Delicate connective-tissue stroma; 2, covering of many-layered cylindric epithelium.

Fig. 2.—**From a Villous Papilloma of the Bladder** (Hemat.-eosin. × 35.): 1, Connective-tissue stroma; 2, many-layered cylindric epithelium; 3, cross-sections of blood-vessels.

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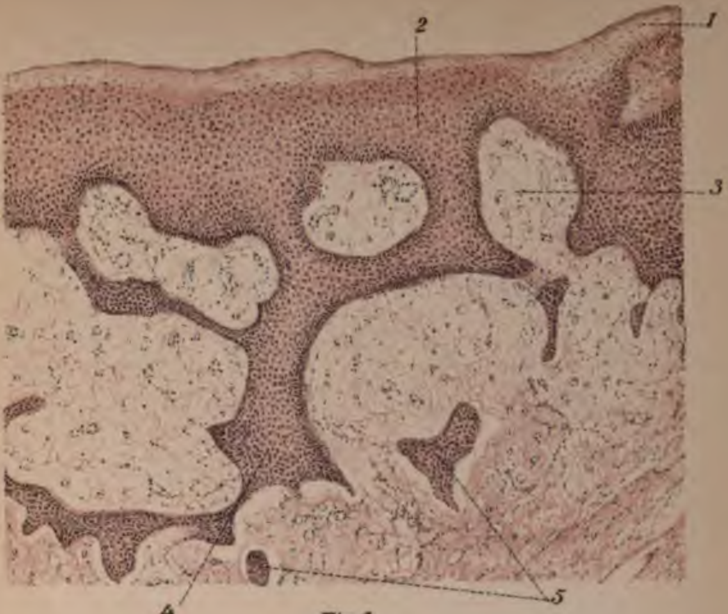
only in particularly favorable sections. These true papillary excrescences must be carefully distinguished from simple folds of epithelium, which may also lead to extensive projections on the inner surface, and, if they are multiple, anastomose with one another so that the cystic cavity is trasversed by a system of communicating epithelial trabeculæ in which no connective-tissue supportive



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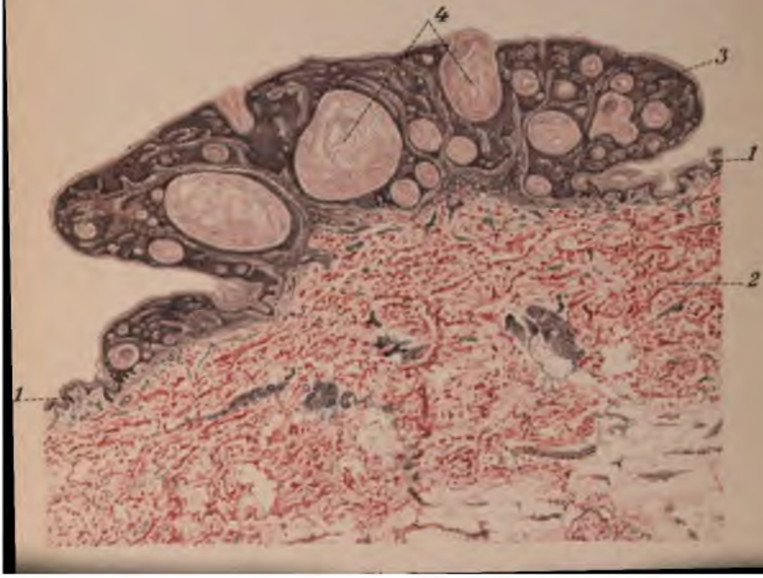

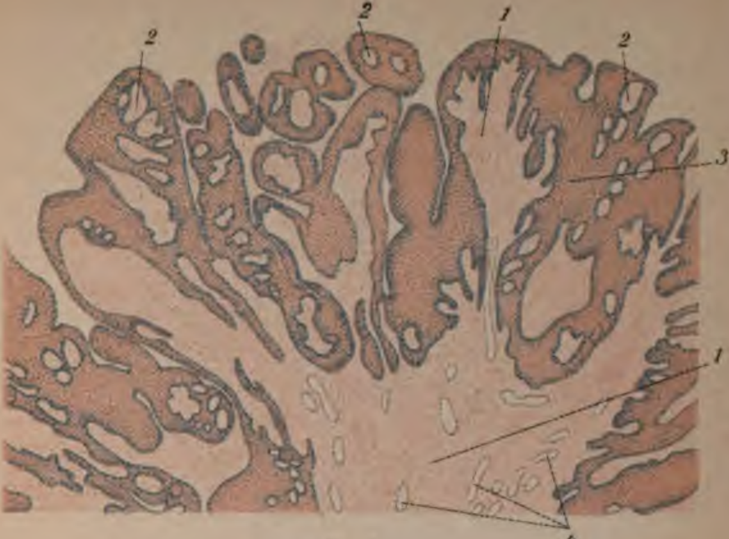

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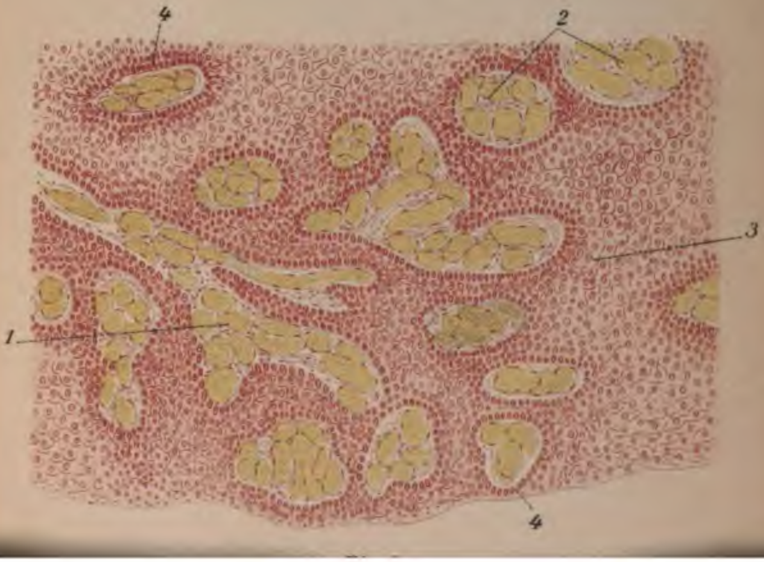

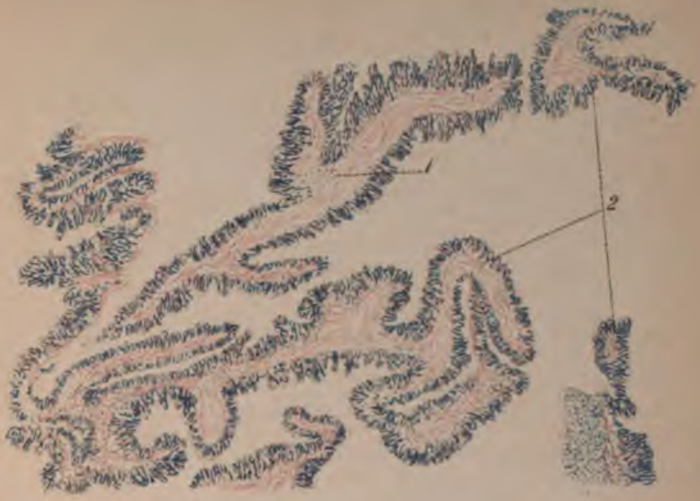

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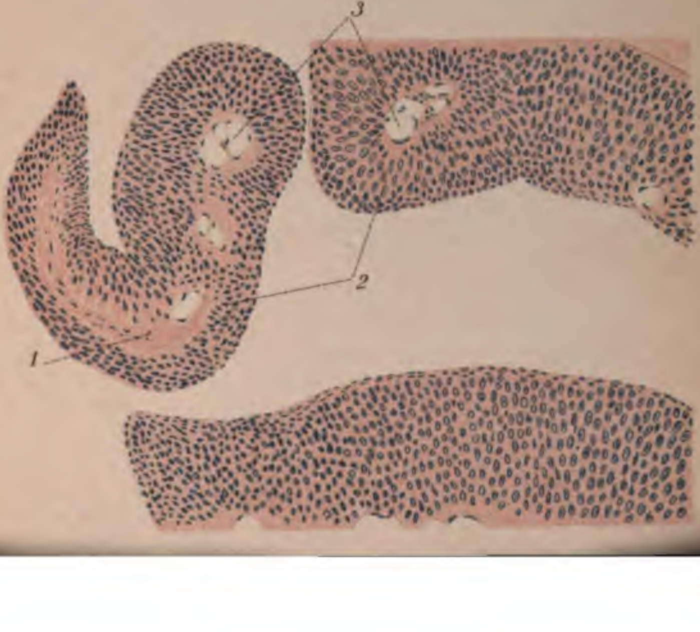


substance is necessarily demonstrable. The cystic contents are often composed of a clear, serous, and sometimes, especially in cystic tumors of the ovary, mucoid material, which may collect in enormous quantities and contains, in addition to ordinary mucin, so-called pseudomucin—*i. e.*, a material that does not coagulate upon the addition of acetic acid.

Cystic adenoma is chiefly observed in the mammary gland and in the ovary. In the former organ the tumor commonly consists of shapeless papillary masses of proliferated connective tissue, covered with epithelium, producing cleft-like invaginations and associated frequently with complete collapse of the lumen (cystadenoma phyllodes). Mucoid degeneration may also occur in the connective-tissue stroma, and in the microscopic picture the latter may appear simply as a collection of isolated, branching cells within a mucoid ground-substance.

Ovarian cysts are either single or multilocular, or the lumen is completely or partially filled with papillary excrescences (*cystoma papilliferum*). The epithelium is usually of the tall cylindric variety; sometimes cilia are observed, at least in some portions of the tumor. On the papillæ, on the other hand, the epithelium is usually arranged in several layers, the individual cells in their active growth crowding and pushing over one another; among them are also found numerous goblet-cells (Plate 14, Fig. 2), which accurately imitate the physiologic mucous-production by means of goblet-cells, except that they are distinguished by their greater number and larger size. Ovarian cysts are usually believed to have their origin in germinal epithelium, although it was formerly believed by many authorities that they originate in Graafian follicles. Some symmetric ovarian cysts are probably due to persistence of the Wolffian duct.

In rare cases the ovary is completely filled with papillary cysts, the proliferations projecting above the surface of the organ; the tumor may spread to the peritoneum, where the same ragged excrescences may be formed as in the cyst.

PLATE 69.

FIG. 1.—**Adrenal Tumor from the Kidney** (**Hypernephroma**) (Hemat.-eosin.): 1, Large polygonal cells, containing an abundance of fat and arranged in tubes; 2, connective-tissue cells in the scanty stroma.

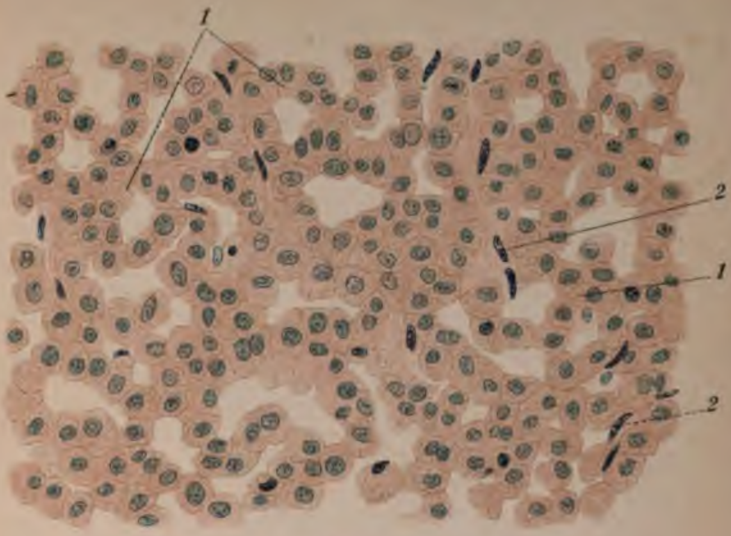
FIG. 2.—**Adenocarcinoma of the Liver Beginning in the Bile-ducts** (Hemat.-eosin. × 100.): 1, Liver-tissue; 2, many-layered epithelial tubes growing into the liver-tissue.

Congenital cystic tumors occur in the liver and kidneys; in the latter they may be so large as to form an obstacle to labor.

An external resemblance exists between adenoma and tumors which originate in the suprarenal glands or in dislocated portions of those organs. These tumors were formerly often described as sarcoma or lipoma, and sometimes as endothelioma. They are due not to genuine new formation of glands, but to proliferation of cells similar in character to those which normally occur in the cortical substance of the suprarenal capsules. If the tumor is unusually large or metastasis takes place, the original cell character may undergo more or less extensive metaplasia, so that the origin of the tumor cannot always be determined by a mere examination of the metastatic growth.

The suprarenal capsules are occasionally the seat of sharply circumscribed, soft nodules, usually of a yellowish color when seen with the naked eye, which Virchow designated **struma suprarenalis.** They are composed of large, polygonal cells, collected to form spheric and tubular masses, with an exceedingly small amount of intercellular substance. As a rule, a few endothelial cells derived from capillaries can be demonstrated in the intervals between the large, tall tumor elements. Quite frequently the cells contain an abundance of fat-droplets. Glycogen has also been demonstrated repeatedly within these cells. Aberrant portions of suprarenal bodies are quite common. They are found chiefly on the surface and within the substance of the kidney, and consist of flat, yellowish nodules situated beneath the capsule, and varying in size from

Tab. 69.



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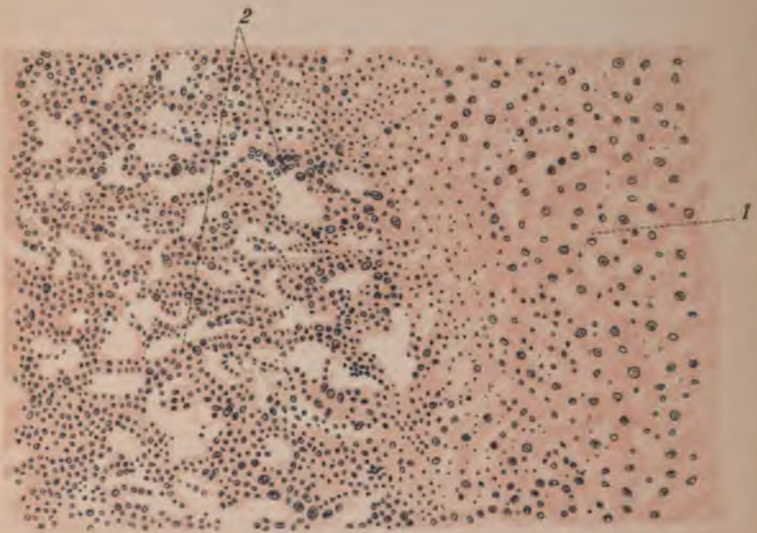

Fig. 2.

that of a hemp-seed to that of a lentil. Sometimes they are multiple and entirely surrounded by cortical substance, thus becoming completely isolated within the interior of the organ. Such nodules are sometimes seen in the peritoneum, in the sexual glands, on the broad or round ligament, on the spermatic cord, or, more rarely, in the liver (Oberndorfer). The misplaced islands of suprarenal capsule may themselves lead to the formation of tumors after the type of struma suprarenalis, and these tumors may attain a large size and lead to metastases in distant portions of the body. As the epithelial character of the cells has not been definitely proved, we cannot designate these structures adenomata, although the tumor elements in many places are collected in tube-like structures. For the present the term *suprarenal tumors* or *hypernephroidal tumors* seems preferable; the name *hypernephroma* has also been proposed. In large tumors of this kind retrogressive metamorphosis is usually quite extensive. Thus, the cells may undergo such marked fatty change that the entire tumor presents an intense yellowish color and a semisolid consistence like that of butter. In addition it is often found that parts of the soft tumor-mass have been destroyed by hemorrhage. In the surviving portions the cells are large, the protoplasm completely filled with vacuoles, and of a frothy structure. Examination of a recent specimen shows the presence of an abundance of glycogen. The nuclei contain a fairly thick network of chromatin, and the cell-membrane is often quite distinct on account of the excessively pale color of the cell-body. The microscopic picture thus often resembles that of vegetable cells. In metastatic growths irregular cords of cells, as well as spheroid aggregations, are discernible, surrounded by scanty connective tissue. This lends to the picture the greatest resemblance to a carcinoma. From the clinical standpoint also this resemblance is sometimes extremely marked, as multiple metastatic growths may appear in many organs at the same time and the neighboring tissue may be destroyed. Sometimes the metastatic growths present a distinct adenomatous or even cystadenomatous structure. The cells are cuboidal in shape, and show a distinct epithelial arrangement, while the lumen of the cyst is often filled with blood.

Carcinoma.

Whereas in the epithelial neoplasms discussed so far a typical relation between epithelium and connective tissue is always demonstrable, the former always following the latter, in the case of epithelial tumors, which show a greater departure from the normal type, the epithelium is to a very large extent independent of the connective tissue. The groups of epithelial cells grow without regular physiologic order, invade the surrounding tissues, and manifest a tendency to spread beyond bounds. These tumors are known as carcinoma.

They originate in lining or glandular epithelium—that is, in the cells of active organs. Carcinoma may result also from preëxisting and previously typically arranged epithelial tumors, as a consequence of changes in the nature of their growth, the ultimate causes of which are still a complete mystery. Sometimes islands of epithelial tissue which have become displaced during fetal life and have never formed a part of the complex of functionating organs, being in a sense superfluous remains, may become the matrix of carcinomatous tumors.

As frequently observed, epithelial tumors require for their existence a certain quantity of vascular supporting tissue. They are, therefore, never quite independent of the latter, and in this sense carcinomata are also *organoid tumors*, in which the epithelial tissue is comparable to the parenchyma of organs. The stroma always consists of a network, the large or small meshes of which contain the groups of epithelial cells in "alveolar arrangement." The characteristics of a carcinoma therefore are the alveolar structure and the epithelial arrangement—that is, the complete absence of any connective tissue between the individual cells of the alveolar contents. In this respect only are the parenchymatous elements of the tumor like epithelial cells. Other points in the diagnosis of carcinoma are the demonstration of irregular, atypical groups of cells and active invasion of the surrounding tissue by the epithelium. Sometimes the stroma of a carcinomatous tumor represents nothing but the remains of the interstitial portion of the tissue attacked by the morbid growth. In such a case it is the preëxisting connective tissue that contains within its meshes the groups of proliferated epithelial cells, and quite often the parenchymatous portions which the connective tissue originally supported are destroyed. It is not rare to find at the edge of the carcinomatous growth, along the invading tumor-cells, remains of the original organ, severed from their natural connections and in process of destruction by the advancing tumor. It should be emphasized again and again that carcinoma does not owe its growth and extent to a progressive, uniform degenerative growth of the affected tissue. Parenchymatous cells are not converted into cancer cells, nor do they undergo "cancerous degeneration," as was formerly believed by many authorities; on the contrary, the latter remain entirely passive, and the tumor, which has originated at a definite point, continues to develop "unicentrally" in its irresistible advance into the surrounding tissue.

The connective tissue of the invaded organ, which becomes in a sense subservient to the tumor and is utilized to further its growth, of course, also undergoes certain changes, usually in the nature of a reactive inflammatory manifestation. First, it becomes the seat of more or less pronounced small-cell infiltration, which is well developed at the limits of almost every carcinoma. The invading tumor in a way represents a foreign body, under the influence of which inflammatory processes take place. Emigration of colorless blood-cells and proliferation of fixed connective-tissue cells, associated with enlargement and multiplication, take place, and sometimes the fibrous portions also undergo a considerable increase. The character of the inflammatory phenomena depends upon the intensity of the irritation produced by the ingrowing tumor. If, as in the case of extensive and insufficiently

PLATE 70.

FIG. 1.—**Adenocarcinoma from the Rectum** (Hemat.-eosin. × 42.): 1, Superficial epithelium; 2, branching gland-tubes; 3, the same, filled with epithelium; 4, stroma.

FIG. 2.—**Adenocarcinoma from Parotid Gland** (Carmin. × 180.): 1, Gland-tubules; 2, many-layered epithelial lining of the same; 3, solid strands of epithelium.

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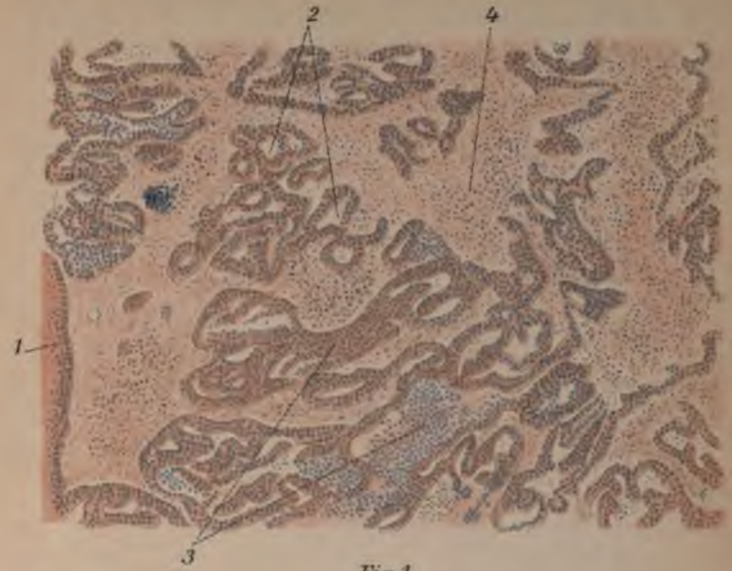
nourished masses of epithelium, degenerative phenomena are well marked in the tumor, the resulting chemotactic influence manifests itself in the flooding of the invaded tissue by leukocytes with fragmented nuclei, which may be so densely packed as to give the impression of a purulent, connective-tissue infiltration. In other cases the "small-cell infiltration" is represented chiefly by lymphocytes, plasma-cells, and sometimes by unusually abundant eosinophile or mast-cells. The proliferative phenomena in the connective tissue are also subject to great variations, and may at times lead to so tremendous an increase of the connective-tissue cells as to give the tissue an embryonal character. This process has been described as a sarcomatous degeneration of connective tissue, and the tumor produced in this way has been designated "*carcino-sarcoma*."

It is not denied that reactive phenomena may sometimes be observed in the parenchymatous portions of the affected tissue, and under certain circumstances it may appear as if these inflammatory elements had a share in the building-up of the tumor, but such proliferative processes have no greater significance than in other kinds of inflammatory changes. At most they lead to a temporary cellular increase and are immediately followed by retrogressive metamorphosis, which later causes their complete destruction.

In many cases, however, the atypical epithelial neoplasm is forced to find its own supporting and vascular tissue. This is the case whenever the growth of the tumor is "exstructive"—that is, when the tumor projects above a natural level or grows into a preformed cavity. The pro-



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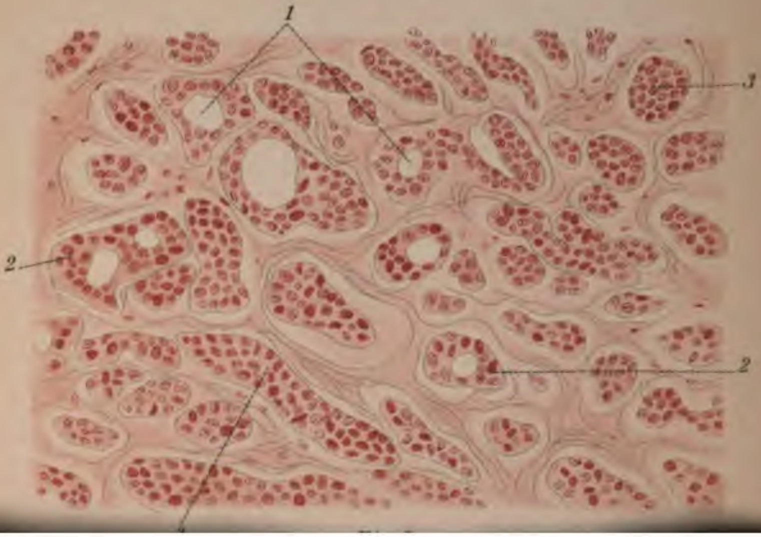

liferation of epithelium in such cases is accompanied by an abundant new formation of connective tissue and blood-vessels, in exactly the same way as in pathologic organization and in the regeneration of connective tissue. The proliferating interstitial tissue, of course, becomes the seat of continued mitotic cell-division of fibroblasts and endothelium, while at the same time the colorless elements of the blood continue to increase in the granulation-tissue. The epithelial cells, which represent the tumor-parenchyma, push their way into the spaces of the connective tissue, utilizing at first chiefly the preëxisting lymph-clefts, but later also other cellular spaces void of endothelial investment. So long as the continuity of the growth is preserved—*i.e.*, so long as passive transplantation of tumor-particles has not taken place by means of the blood or lymph circulation—the rapidity of growth always depends on the rate at which proliferation of tumor-cells takes place. The microscopic picture gives us a good criterion for the rate of growth in the abundance of the mitotic figures found at the border of the tumor. Hence the alveoli, nests, or tube-like aggregations of epithelial cells, which are always found in some sections, are to be regarded as portions of cell-cords or root-like processes, anastomosing with one another or with the tumor node itself. In serial sections, or when the tumor is reconstructed in wax, it appears conclusively that all the alveoli or cords communicate with one another. Carcinoma is, therefore, characterized by a distinct tendency to infiltration, and thus differs from many connective-tissue tumors, which have a tendency to expand; the increase in size always takes place by peripheral apposition of new elements formed by repeated division at the edge of the growth.

The shape of the epithelial cells that enter into the structure of a carcinoma is extremely variable. As frequently observed, the shape of the cells can never be utilized as a basis for a diagnosis. It is impossible to determine from a single or from several isolated tumor-cells whether they originally belonged to a carcinoma or to a sarcoma; it is only by studying their mutual relations to one another that the question can be solved. But in the main, carcinoma contains flat, cuboidal or cylindric types of cells, depending on the point of origin of the tumor (see below). The original form may be preserved for a long time; it is occasionally preserved not only throughout the mother tumors, but also in daughter tumors, so that examination of the metastatic growth affords a clue to the character of the epithelium from which the tumor started. But this is by no means a rule, and exceptions are quite common. Quite frequently the epithelial cells experience flattening or modeling by reciprocal pressure; and, in the main, this modeling is the more pronounced the greater the intensity of the proliferative processes and the larger the groups of alveoli. This mechanical effect of the cells on one another may in itself lead to considerable deviations of the cells from the original character of the epithelium from which the tumor originated; moreover, the shape of the cells is affected by the nature of their growth; even in the beginning they often present marked deviations from the original morphology of the cells of the matrix. From the outset a tendency to metaplasia may manifest itself in the tumor-cells, and this may be so marked that the examination of individual tumor-elements, or even of parts of metastatic growths, fails to give any information as to the character of the matrix. Of course, the morphologic character of the proliferating cells does not undergo any higher development; the cells do not become more highly differentiated. On the contrary, they usually return to a lower, more indifferent stage; thus, for example, cylindric cells are converted into polygonal or cuboidal elements, or occasionally into squamous cells; but the inverse process never occurs. As we have already learned in the general portion on Tumors, the cells during this metaplasia may develop certain qualities which they did not possess before. For example, cornification may take place in the metastatic growths derived from a tumor consisting of cylindric cells; or mucous-production may be seen in daughter-tumors derived from a glandular cancer which originally did not produce mucus. This phenomenon must be regarded as a degenerative process. On the other hand, the tumor-cells may retain for some time the specific characters of the matrix, and, under certain circumstances, it is justifiable to speak of functional processes in connection with tumor-cells. For example, the power to form colloid substance may persist for a certain time in carcinoma of the thyroid gland; that of producing mucus in cylindric carcinoma of the gastro-intestinal canal; and even the production of bile in carcinoma of the liver. In the main, however, retrogressive changes gain the upper hand as the epithelial cells continue to proliferate, and these changes may sometimes develop with extreme rapidity and involve enormous areas. As regards cell-division alone, carcinomata as well as sarcomata present a number of anomalies which have already been sufficiently described in another place (p. 213). Similarly the reader is referred to what has been said in the same place about various forms of degeneration—fatty, mucoid, calcareous, etc.

In carcinoma the quantitative relations between stroma and parenchyma are variable. The meshes of the connective tissue are sometimes extremely large, so that the masses of epithelium form by far the greater portion of the tumor. In fact, the development of stroma may be so slight and insignificant that it is almost overlooked at the examination, in which case the tumor, of course, is of a soft, medullary consistence. In these tumors the paucity of connective tissue is not due solely to the preponderance of the protoplasmic substance of the epithelium over the connective-tissue fibers, but also to retrogressive metamorphosis, especially to insufficient nutrition of the large epithelium complexes by the imperfectly developed blood-vessels. These tumors are designated *medullary carcinomata*. Conversely, the fibrous tissue may be well developed, in which case the cavities are small and usually cleft-like in shape. The nests of cells may be arranged in long narrow lines alternating with strands of stroma, and this results in the production of a hard cancer or *scirrhus.*

FIGURE XXVIII.

Scirrhus of the Mammary Gland (× 70.): 1, Dense masses of connective tissue; 2, linear masses of epithelium.

These scirrhous forms (Plate 74, Fig. 1, and Fig. XXVIII.) are prone to be formed when the velocity of the growth is not great and sometimes when the tumor invades tissue which is naturally hard and sclerotic in character. Sometimes the destruction of parenchymatous portions in parts of the tumor may be followed by fatty change or other retrogressive metamorphosis and partial cicatrization, with the secondary formation of a dense, fibrous connective tissue and the production in this way of scirrhotic areas in the tumor.

A carcinoma in which the width of the alveoli is approximately the same as the average width of the connective-tissue septa of the stroma is known as a *simple carcinoma*. Epithelial tissue and connective tissue in such a tumor are about equal in quantity.

Owing to the multiplicity in the forms of carcinoma-cells it is difficult to utilize that feature as a basis for classification, and although this has been done repeatedly, and the terms squamous carcinoma and cylindric carcinoma have been used, it does not seem to be practicable, because the determination of the cell variety present in a given case is frequently most perplexing, and because the shape of the cells may vary greatly in the same tumor or in a metastatic growth as compared with the mother tumor. When a certain type is well marked, it may be justifiable to speak of a squamous carcinoma or a cylindric carcinoma, but, as a general rule, it will be better to base the classification of carcinoma not upon the shape of the cells, but, if possible, upon the points of origin of the tumor (parent tissue). We, therefore, classify carcinoma as follows: (1) Epithelial carcinoma, of the skin and of the mucous membranes, covered with squamous epithelium. (2) Epithelial carcinoma of the mucous membranes covered with cylindric epithelium. (3) Carcinoma of gland-cells (or gland-ducts).

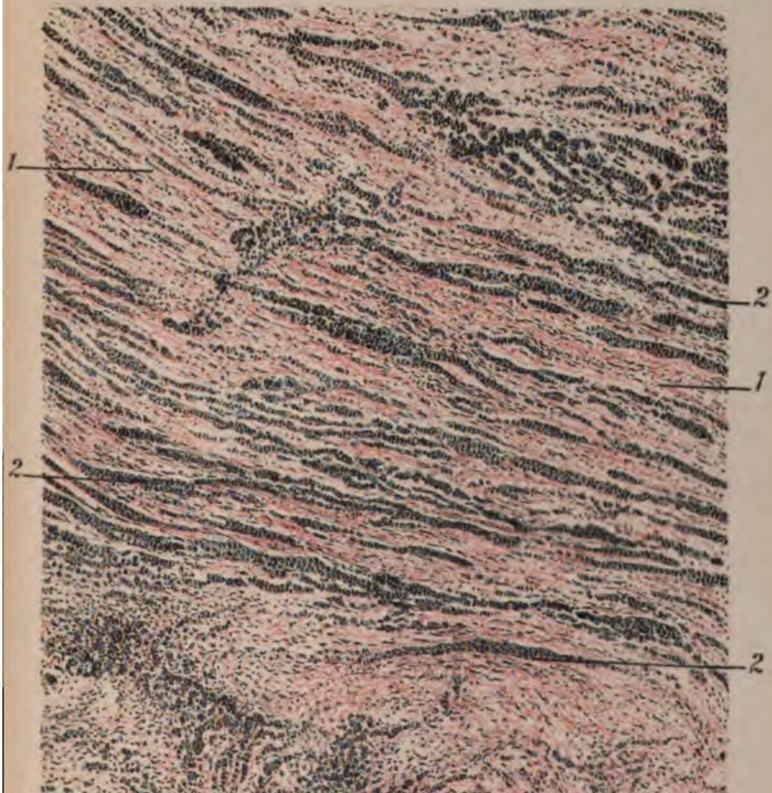

Fig. XXVIII.

1. In cancers originating from the skin or from mucous membranes covered with squamous epithelium the squamous character of the cells, especially in the early stages of the growth, is well preserved.[1]

The tumor usually originates in the epithelial plugs which dip down between two papillæ into the deep layers of connective tissue. Sometimes there is no doubt that, owing to primary changes in the connective tissues of the skin or mucous membranes, certain atypical proliferations are present even before the epithelial neoplasm develops the character of a carcinoma; the occurrence of such atypical proliferation has already been referred to in connection with the epithelial regeneration (Plate 66, Fig. 1). Atypical epithelial proliferation of this kind is frequently seen in scars and at the edge of ulcers, but it would be too much to say that in every case the primary presence of inflammatory changes in the subepithelial tissue is responsible for the development of a carcinoma, as various authors have recently done. It is an absolute principle that epithelium plays an active rôle in the development of carcinoma even during the initial stages; for even if it is assumed that inflammatory processes may be responsible for the appearance of dislocated or aberrant groups of epithelial cells in the connective tissue, which later *may* form the starting-point of carcinoma, this does not explain why in these cases the displaced epithelium suddenly develops the peculiar property of atypical, unlimited proliferation.

It appears, then, that solid plugs of epithelium dip down into the connective tissue; they undergo repeated division and form branching masses, which are again united by the formation of bridge-like processes, and thus a network of epithelial strands gradually extends deeper

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[1] The term *cancroid* was formerly used to describe these forms. So long as cancers were believed to grow from connective tissue those forms in which the epithelial character was at once recognized were regarded only as cancer-like or cancroid neoplasms. The term cancroid is, therefore, not justifiable at the present day, since we know that all cancerous tumors without exception must originate from epithelial cells.

FIGURE XXIX.

Horny Carcinoma from a Section of the Toe (Recent Teased Preparation. × 300.).

FIGURE XXX.

Squamous Carcinoma from the Scalp with Advanced Degeneration of the Cells (× 500.).

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and deeper into the tissue, undermines the normal epithelium laterally, and in many places forms connections secondarily with the latter. As the tumor continues to grow it not infrequently becomes raised above the level of the adjoining skin or mucous membrane, and nodular or hemispheric elevations are formed. The main body of the cell usually exhibits the character peculiar to the elements of the rete Malpighii, the stratum spinosum. Sometimes the spines and ridges on the individual cells are distinctly discernible even in extensive proliferations; in fact, they may be unusually well developed and distinctly show the protoplasmic processes bridging over the lines of cement.

Quite frequently all the normal layers of the epidermis are reproduced in the tumor. In such cases the strands which dip down into the tissue, as a rule, exhibit a concentric stratification, the layers of which, in transverse sections, appear circular and from without inward exactly reproduce the structure that is so well marked in the normal epidermis from below upward. Sometimes the concentric arrangement is especially well developed in some of the larger strands, giving rise to the formation of structures that suggest the successive layers of an onion; as the inner portions of such a structure are usually cornified, they are designated *cancroid pearls* or *cancer pearls* (Plate 71, Fig. 1; and Plate 72, Fig. 1). The outer portions of these concentric bodies are usually formed of individual cells which correspond to the basal, germinal layer of the normal epiderm. Next to this is a broad layer of polyhedral or spindle-shaped epithelial cells, which exhibit an accumulation of keratohyaline granules in their protoplasm, progressively increasing in quantity from without inward. The inner layers are,

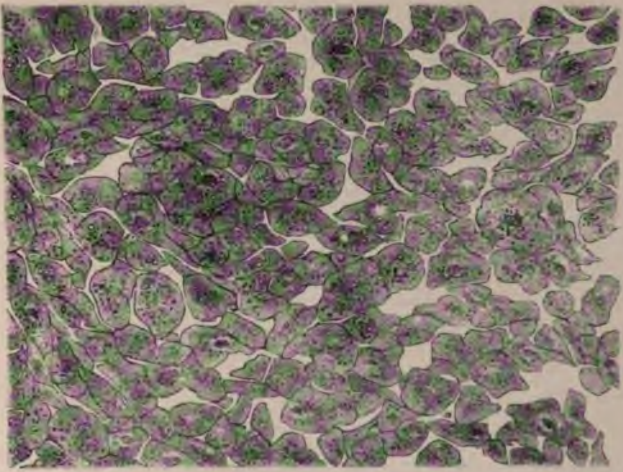

Fig. XXIX.

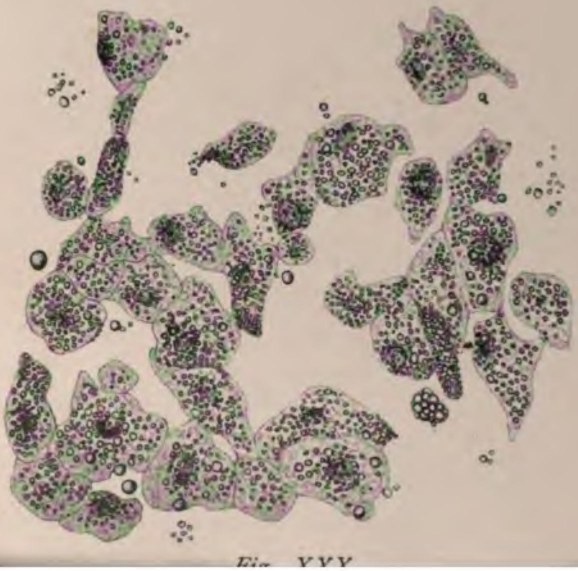

Fig. XXX.

as a rule, formed by flat, completely cornified scales, absolutely void of nuclei. The center of one of these epithelial pearls sometimes contains peculiar degeneration-products of cells, which tinctorially exhibit a marked contrast to their surrroundings (Plate 71, Fig. 2); for instance, they stain very deeply with eosin or fuchsin. In addition to the concentric, imbricated epithelial cells, spheric, drop-like degeneration-products of such cells may be present. Occasionally hyaline or colloid degeneration may be present, as well as débris of epithelial nuclei or of leukocytes that have invaded the interior of the pearls. All these structures, which somewhat resemble foreign bodies, have repeatedly been regarded as the parasites of carcinoma by the supporters of the parasitic theory of the etiology of cancer.

This form of carcinoma, which is accompanied by the formation of epithelial masses in the shape of plugs, strands, or trabeculæ, may be said to represent the regular type of the squamous-cell carcinoma; although forms occasionally occur in which irregular accumulations of squamous epithelial cells, modelled by mutual pressure, are produced, and in which it is impossible to recognize any concentric arrangement and any repetition of the physiologic structure in the stratification. The squamous character of the epithelium in these forms may, however, show itself distinctly in the extensive cornification which takes place (Plate 72, Fig. 2); in fact, the tumors may consist mostly of horny epithelium. In that case only a few of the epithelial cells retain their nuclei. The nuclei are surrounded by innumerable, irregular, usually circular, sometimes dentate, keratohyaline granules, which take a dark stain with hematoxylin or carmin. In addition, cells are found containing horny material, either at the edges only or in a large portion of the protoplasm. Sometimes the cornification in large groups of these squamous cells is associated with a fatty degeneration of the cells. In recent, teased preparations they are then found filled with innumerable fat-droplets, and even in a stained section the round vacuoles are still discernible within the

PLATE 71.

FIG. 1.—**Carcinoma of the Penis** (Hemat.-eosin. × 80.): 1, Epithelial plug with flattened outer layer (2); 3, cornified inner layer; 4, stroma.

FIG. 2.—**Structures Resembling Parasites Within Carcinoma Pearls, from a Carcinoma of the Lower Lip** (Hemat.-eosin. × 640.): 1, Nuclei of large flat epithelial cells; 2, flat epithelia, some of them suggesting in their arrangement the successive layers of an onion, intensely stained with eosin; 3, débris of epithelia and of leukocytes that have invaded the pearl.

PLATE 72.

FIG. 1.—**Epithelial Cornification in a Skin Cancer of the Penis** (Hemat.-eosin. × 640.): 1, Large polygonal and flat imbricated epithelial cells; 2, keratohyaline granules within the same; 3, epithelial cells that have lost their nuclei; 4, cornified inner zone.

FIG. 2.—**Cornification in a Carcinoma of the Skin of the Big Toe** (Carmin-Gram stain. × 625.): 1, Nucleated epithelial cells with many keratohyaline granules; 2, nucleated cells, mostly in a state of cornification; 3, solid horny masses without nuclei; 4, fat-vacuoles within the same.

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horny cells (Plate 72, Fig. 2). The stroma of the squamous-cell carcinoma is often densely infiltrated with round cells; for these forms are usually in direct communication with the skin or with a mucous surface. When, as the result of maceration or a solution of continuity in the surface, ulceration has taken place, parts of the stroma are particularly likely to be found immediately below the surface. The result is a dense infiltration of the interstitial tissue with round cells, and especially with leukocytes also, which may be so intense that individual portions of the tumor undergo actual suppuration. The epithelial layers are then also thickly infiltrated with leukocytes. The epithelial cells usually undergo marked fatty degeneration, and in this way the superficial portion of the tumor may be exfoliated or consumed by phagocytes, as it were. Sometimes putrefaction of a portion of the carcinoma may take place as the result of the entrance of putrefactive fungi.

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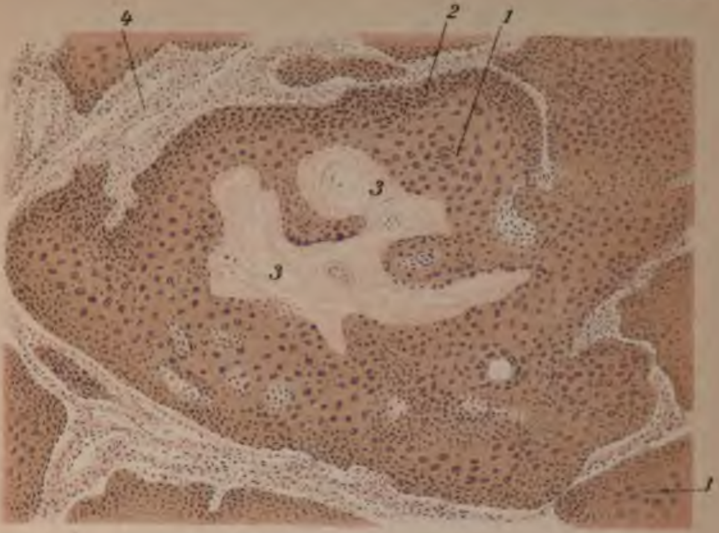

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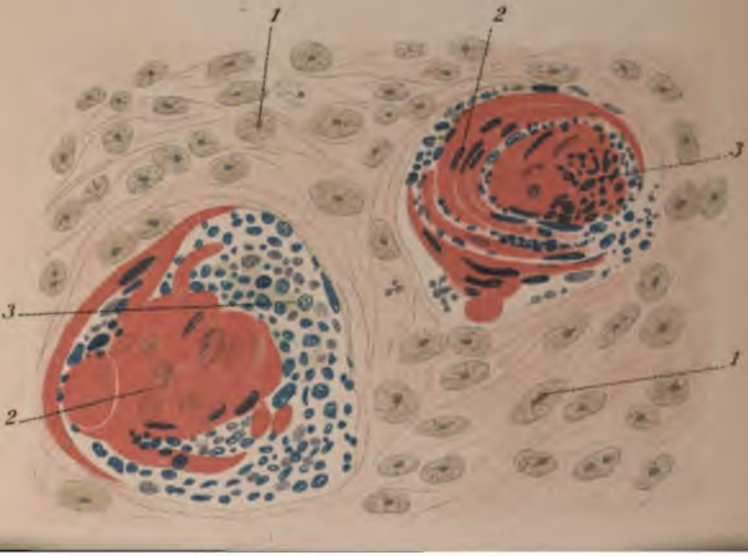

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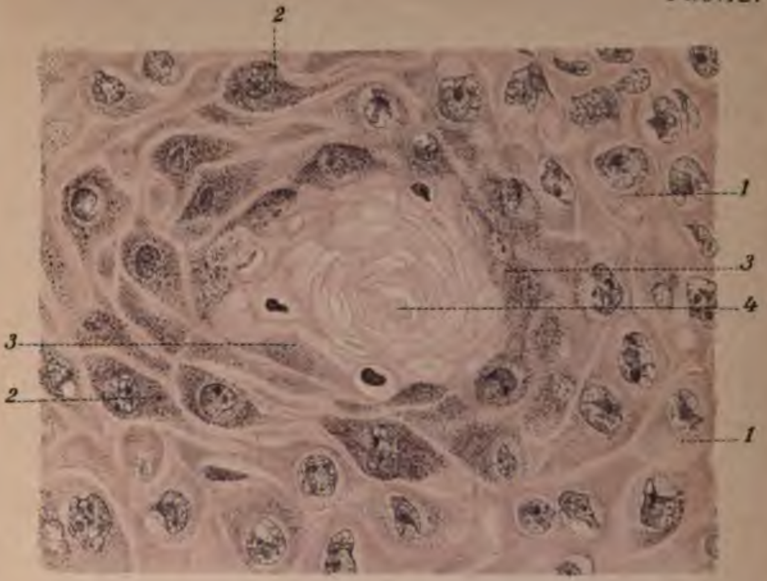

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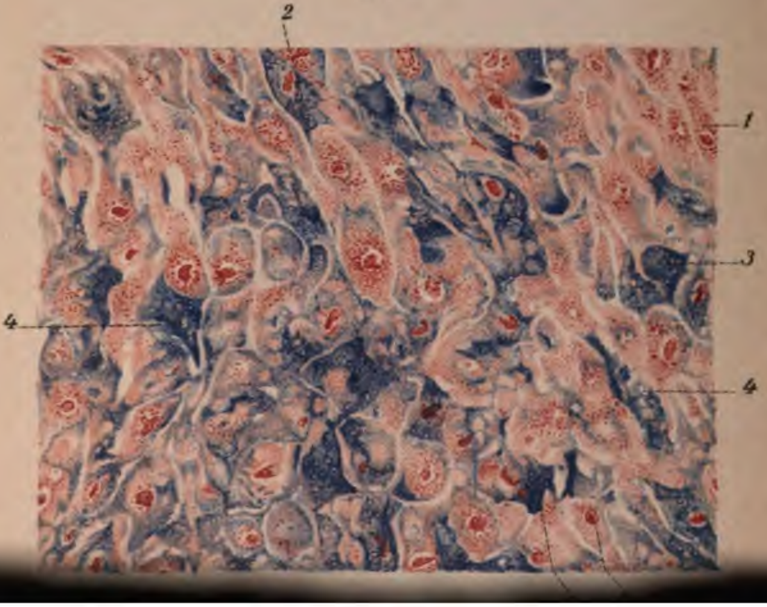

Carcinoma after the type of those just described, with cornification either at the center, in the form of pearly structures or in the form of diffuse deposits of horny material, may originate not only in structures normally covered with squamous epithelium,—*i. e.*, the skin and certain mucous membranes,—but may also occur metaplastically from carcinoma of the trachea, the stomach, the rectum, the uterus, the gall-bladder, etc.; hence the demonstration of horny material proves nothing in regard

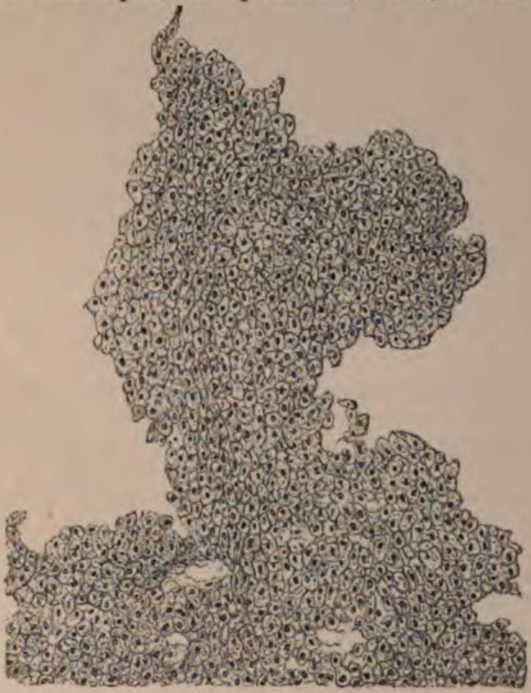

FIGURE XXVII.

From a Polypoid Carcinoma of the Rectum (Recent Teased Preparation. × 70.). Mosaic flattening of the originally cylindric cells from mutual pressure.

PLATE 73.

Fig. 1.—**Simple Carcinoma of the Mammary Gland** (Hemat.-eosin. × 50.): 1, Epidermis; 2, solid communicating epithelial cords; 3, stroma.

Fig. 2.—**Metastatic Simple Carcinoma in the Dura Mater** (Hemat.-eosin. × 150.): 1, Solid epithelial plugs lying within alveoli; 2, stroma.

PLATE 74.

Fig. 1.—**Scirrhus of the Mammary Gland** (Hemat.-eosin. × 50.): 1, Broad masses of fibrous connective tissue; 2, more cellular masses of connective tissue; 3, narrow cancer-alveoli.

Fig. 2.—**From a Simple Carcinoma of the Mammary Gland, with Partial Myxomatous Degeneration of the Interstitial Tissue** (Hemat.-eosin. × 200.): 1, Alveoli filled with epithelial plugs; 2, connective-tissue stroma; 3, part of the stroma in a state of myxomatous degeneration.

PLATE 75.

Fig. 1.—**From a Colloid Carcinoma of the Mammary Gland** (Hemat.-eosin. × 66.): 1, Heavy strands of connective tissue; 2, nests of epithelial cells in a state of mucoid degeneration; 3, epithelial cells after complete mucoid degeneration; 4, alveolar spaces in which gaps have been formed as a result of the hardening of the soft mucoid epithelial cells.

Fig. 2.—**From a Colloid Cancer of the Stomach** (Hemat.-eosin. × 72.): 1, Connective-tissue stroma; 2, epithelial remains; 3, empty alveoli with degenerated epithelial cells.

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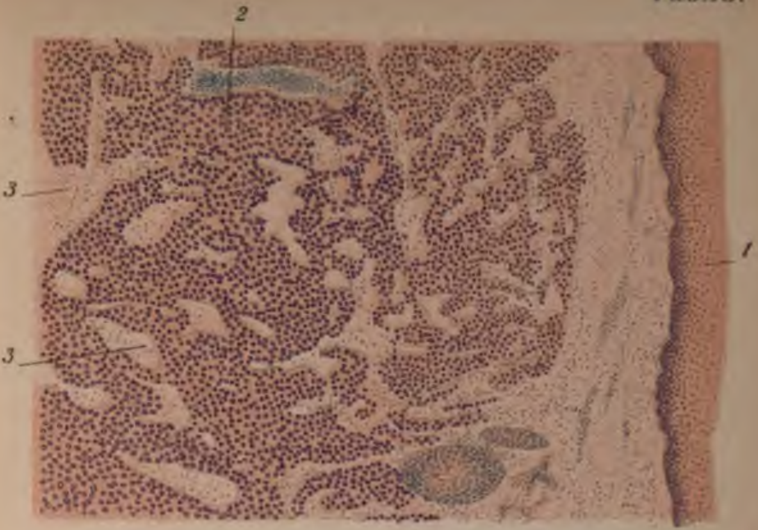
to the nature of the tissue from which such a tumor has sprung.

2. **Carcinoma originating in mucous membranes covered with cylindric epithelium** usually exhibits in its subsequent development a gland-like structure in the arrangement of the epithelial masses. The cylindric epithelium, like the squamous variety, also pushes its way rapidly into the depth of the tissue; at the same time the glandular tubes receive an epithelial covering of several layers and proliferate into the subjacent connective tissue, the submucosa, and the adjoining strata.



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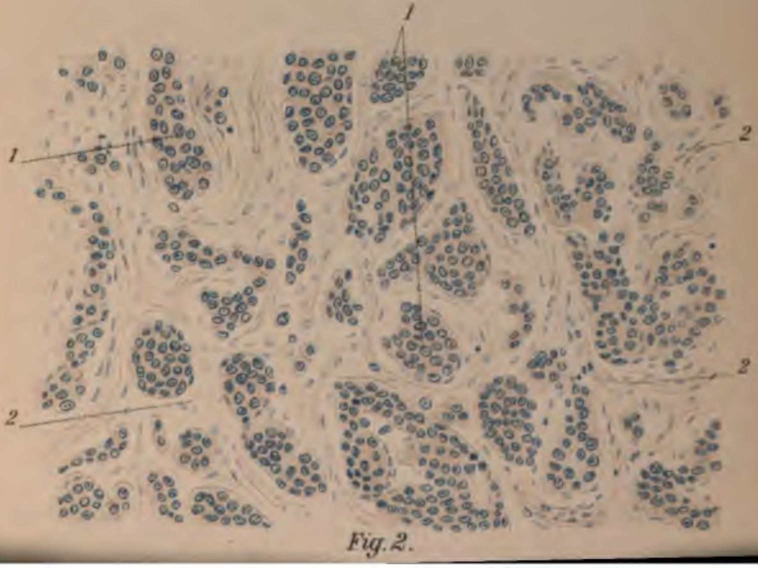

Fig.2.

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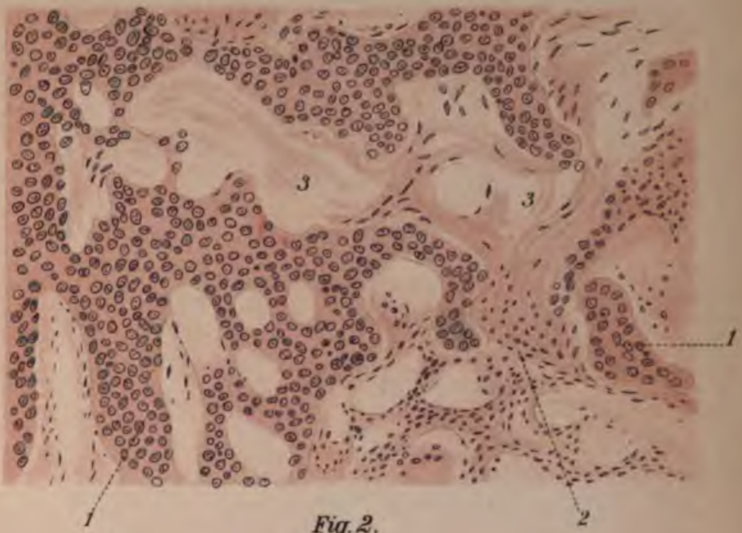

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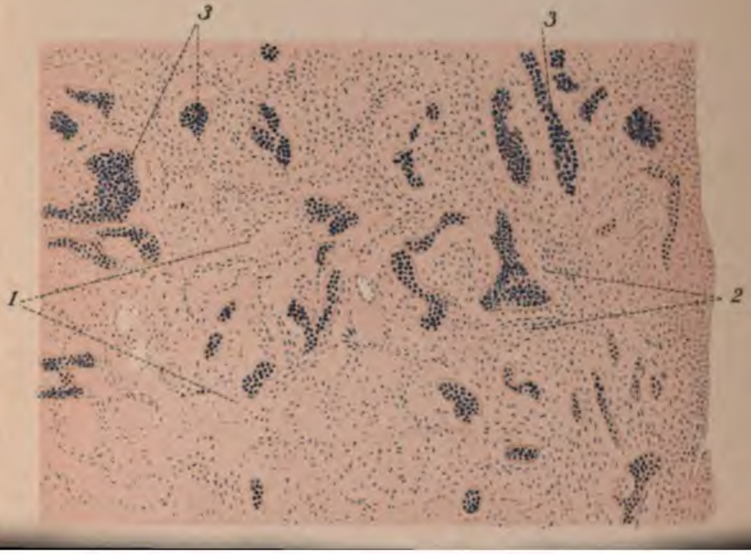

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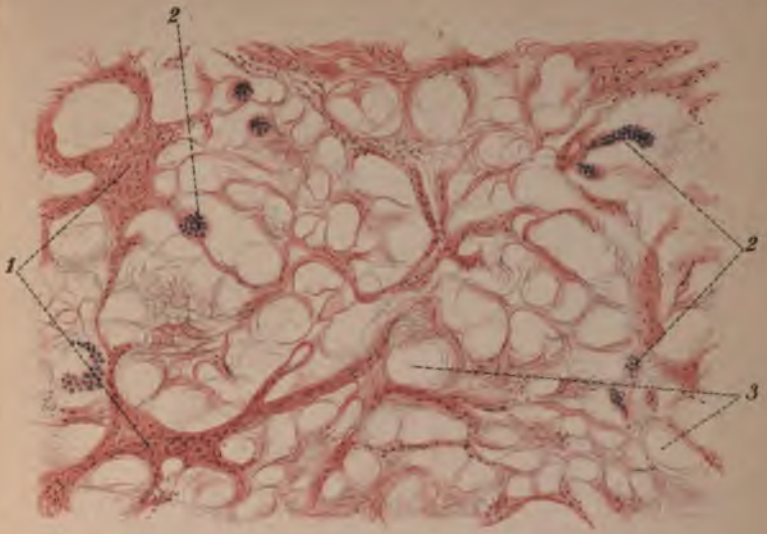

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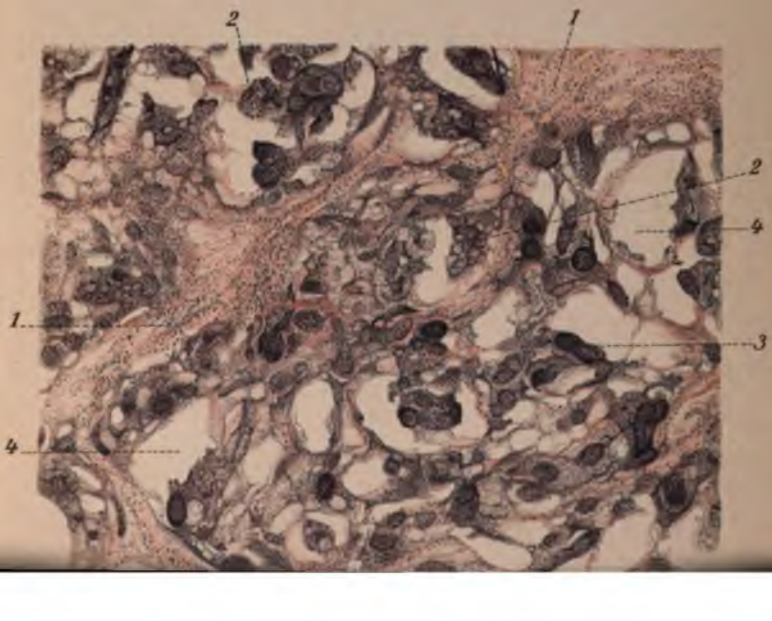


So long as the glandular type is preserved and the connection with the cylindric epithelial crypts of the surface is distinctly recognizable, the term *adenocarcinoma* is used (Plate 72, Figs. 1 and 2). Quite often the glandular character of the cells is preserved distinctly. Even in the carcinoma of this group goblet-cells are often found in large numbers, their development being precisely the same as that which takes place in normal mucous membranes or in the epithelial tumors of typical structure. Primarily typical—*i. e.*, adenomatous or papillary—tumors may become the seat of such adenocarcinoma, the epithelium suddenly, and without recognizable cause, and after the tumor has existed for some time as a clinically benign growth, beginning to undergo degeneration and exhibiting an aggressive attitude toward the neighboring tissues.

By mutual flattening and crowding the cells of such a carcinoma, although originally of a purely cylindric type, may become polygonal or cuboidal. Sometimes the tumors bulge in the form of polypoid excrescences above the surface of the mucous membrane. The growth may, however, be exceedingly rapid, in which case the character of the cells becomes usually more and more indifferent (Fig. XXVII.).

3. The cancers that form the third main division begin in the **epithelial glands of the mucous and skin-glands** or in the **epithelium of the large glandular organs.** These tumors also must be assumed to originate at some definite point, from which the irregular growth into the surrounding tissue takes its beginning, so that the adjoining normal gland-tissue in this case also is destroyed. In the case of glandular carcinoma, which is surrounded on every side by glandular parenchyma and exhibits an expansive growth, there is no reason to suppose that the enlargement is the result of an abnormal growth, progressively involving large complexes of cells, one after the other; glandular tumors also grow unicentrically.

In small glandular carcinomata it is sometimes possible to follow the growth quite accurately; in a circumscribed carcinoma of the breast, for instance, tubules consisting

FIGURE XXXI.

Simple Carcinoma of the Mammary Gland (× 70.). To the left above, normal mammary tissue; below, in the middle, and to the left, a cross-section of an excretory duct; to the left below, a tubule with several layers of epithelium; to the right above, tubules, for the most part filled with proliferated cells; to the right below, large epithelial masses, some of the cells of which are partially degenerated, and between them a densely infiltrated connective and fatty tissue.

PLATE 76.

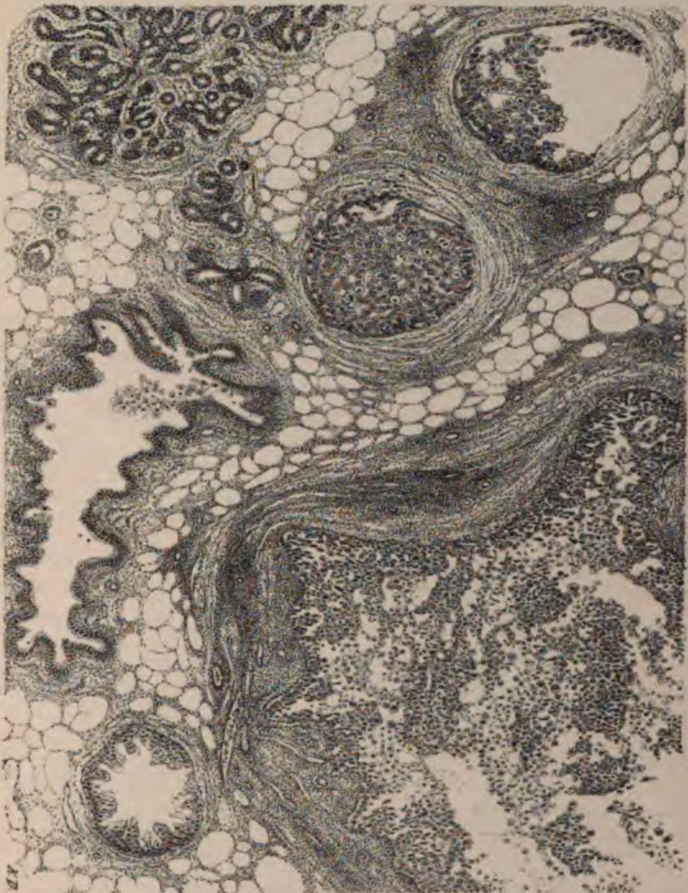
Fig. 1.—**Metastatic Carcinoma in an Axillary Lymph-gland Secondary to a Carcinoma of the Mammary Gland** (Hemat.-eosin. × 90.): 1, Connective-tissue capsule; 2, marginal sinus; 3, cancer-cells in the marginal sinus; 4, degenerated tumor-masses.

Fig. 2.—**Metastatic Carcinoma in a Subperitoneal Lymph-cleft in the Intestine, Secondary to Carcinoma of the Uterus** (Hemat.-eosin. × 42.): 1, Intestinal mucous membrane; 2, submucosa; 3, muscularis; 4, peritoneum; 5, metastatic carcinoma in the subperitoneal lymph-cleft.

FIGURE XXXII.

Peribronchial Carcinomatous Lymphangitis. (Metastatic Carcinoma Nodules in the Peribronchial Lymph-vessels Secondary to Cancer of the Mammary Gland, After Invasion of the Pleural Cavity. × 280.)

of several layers are first observed; gradually they are filled with proliferated epithelial cells, which then break through the surrounding membrana propria, and finally invade the surrounding connective tissue or gland-parenchyma (Fig. XXXI.). Again, therefore, the first step is the formation of cell-tubules, and the term "adeno-carcinoma" might properly be applied to this variety also. Sometimes cystic dilatations appear in the stratified cellular aggregations or complexes from an accumulation of secretion within the lumen, while at the same time the advancing proliferation contributes to the enlargement of the cyst-wall. As a rule, however, the epithelial cells are flattened by mutual pressure and reduced to polygonal



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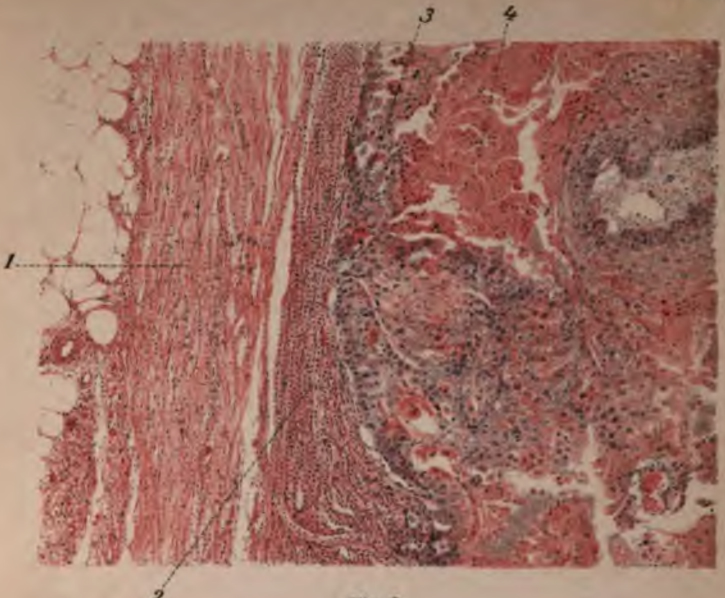

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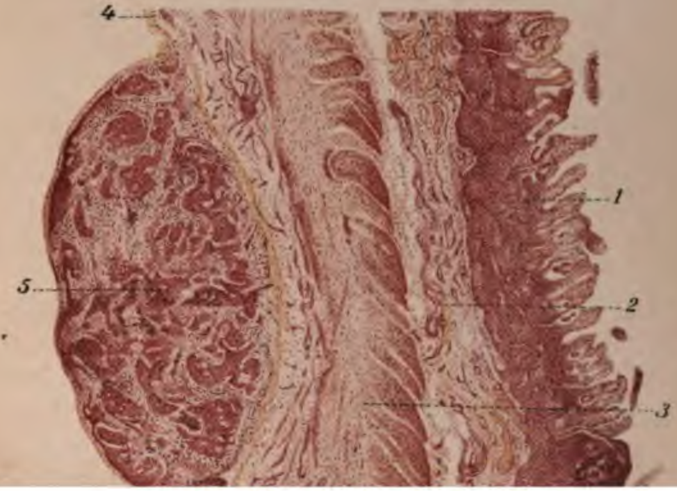

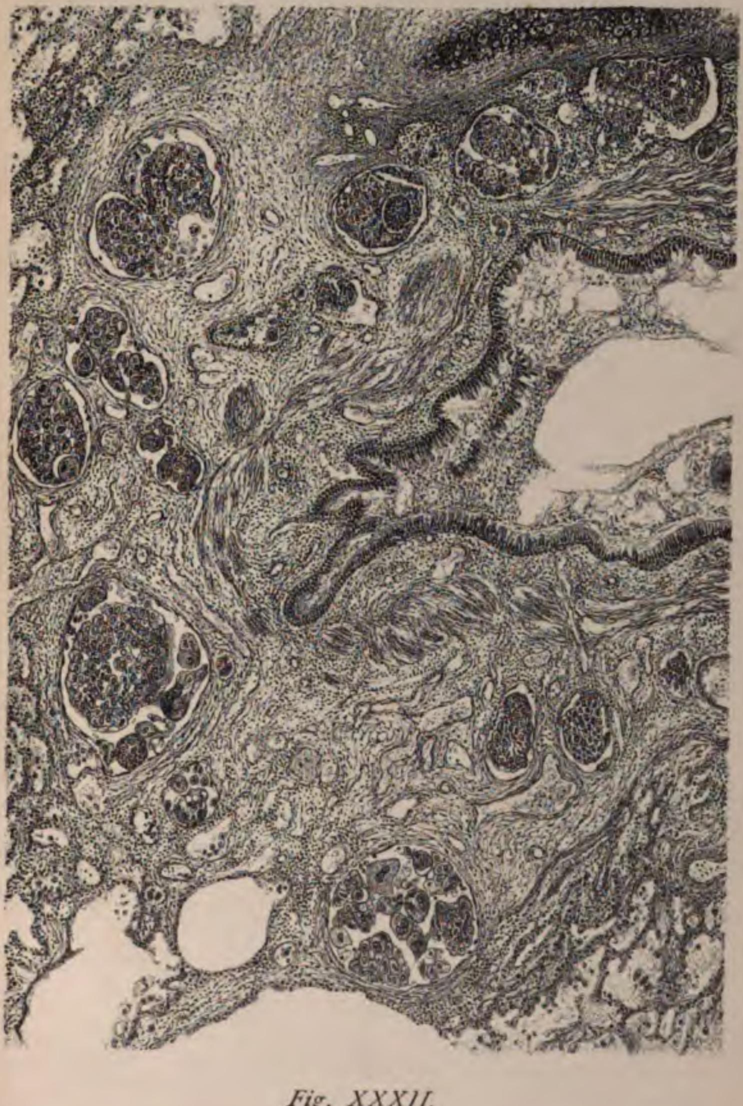

Fig. XXXII.

structures, and these carcinomata furnish the main contingent of the so-called simple carcinomata, in which the proliferation of stroma and tumor-parenchyma goes on uniformly, and solid, communicating epithelial masses of moderate size are produced. Of course, there may be variations in the development of the stroma, resulting in the production of types approaching the soft medullary carcinoma or of scirrhus, in which the connective tissue is more abundant.

The enlargement of the tumor is effected, as stated, by an infiltrating growth, during which additional proliferating groups of epithelial cells penetrate the surrounding tissue. All the individual parts of the tumor are, therefore, in communication, and the growth is continuous. In the course of its progress the neoplasm may enter the lymph- and blood-channels; rupture into a vein is quite as frequently observed as in the case of sarcoma. Particles of the tumor may then be carried by the lymph- or blood-stream to distant areas in the body and, being endowed with an intrinsic power of multiplication, may give rise to a fresh tumor-node of the same type—metastatic tumors are produced. When carcinoma spreads by way of the lymph-stream, retrograde transplantation is frequently observed as a result of occlusion of certain lymph-channels by carcinomatous thrombi or proliferating tumor-masses and partial reversion of the lymph-stream. Sometimes lymph-vessels surrounding a carcinoma are completely injected with masses of epithelial cells (*carcinomatous lymphangitis*). This is particularly the case in the lymphatics of the serous membranes and of the lungs.

In such cases it is often found that the vessels are completely stuffed with closely packed epithelial cells. The part played by the endothelium in this process is entirely passive. Either it atrophies or, if the carcinomatous emboli are arrested and thus obtain a firm footing in the lymph-vessel, as it were, it may proliferate secondarily and contribute part of the stroma of a metastatic tumor produced in this way (Borst). In the lungs a regular injection of the lymph-vessels with carcinoma cells fre-

PLATE 77.

Fig. 1.—**Carcinomatous Embolus of the Lung in a Case of Primary Carcinoma of the Uterus** (Hemat.-eosin. × 280.): 1, Pulmonary alveoli; 2, muscular layer of the pulmonary artery; 3, thrombus consisting of blood-platelets and leukocytes, attached to the muscular layer; 4, loose epithelial cells.

Fig. 2.—**Carcinomatous Thrombus in a Branch of the Portal Vein in a Case of Primary Cancer of the Stomach** (Hemat.-eosin. × 280.): 1, Liver-tissue; 2, wall of branch of portal vein; 3, loose carcinoma cells lying free within the lumen of the blood-vessel.

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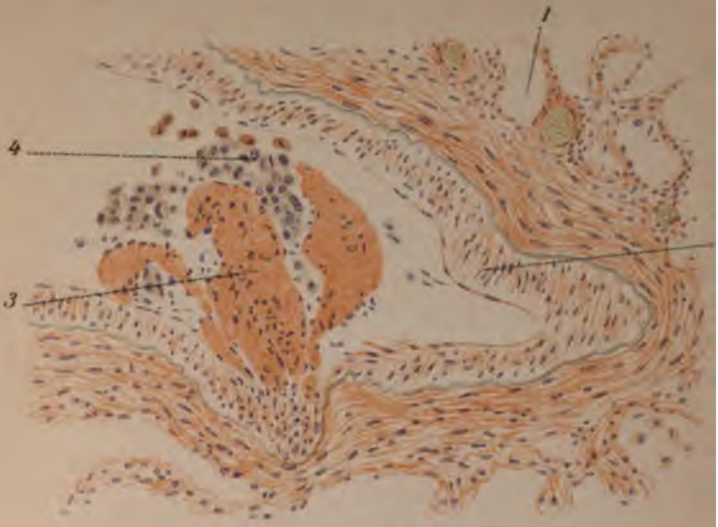
quently takes place, especially when the tumor has invaded the pleural cavity and has given rise to an exudative pleuritis. In this case the tumor-cells suspended in the exudate are absorbed by the lymph-vessels and proceed to proliferate in their channels. The peribronchial and perivascular lymph-clefts are often found filled with tumor-thrombi (Fig. XXXII.) (compare also Plate 76, Fig. 2).

When portions of carcinoma are carried by the lymph-stream as far as the lymph-glands, they become deposited and first multiply in the sinuses, especially in the marginal sinus. The latter may be completely filled with closely packed epithelial masses, while the inner portions of the gland-tissue remain intact. As the tumor-cells continue to grow the lymphocytes are crowded out, the follicles disappear, and the stroma is produced from the glandular reticulum; later the tumor breaks through the capsule of the lymph-node.

Carcinoma may invade the circulation in one of two ways: it may either proliferate into the capillaries and the epithelial plugs may continue to grow within these vessels until they reach the veins, or the thin-walled veins themselves may become infiltrated by the tumor, usually by way of the perivascular lymphatic vessels; when tumor-particles, after they have broken through the endothelium, are washed away. When the greater circulation has been entered, the metastatic masses are carried to the right heart and lead to embolism of the pulmonary vessels.

Tab. 77.



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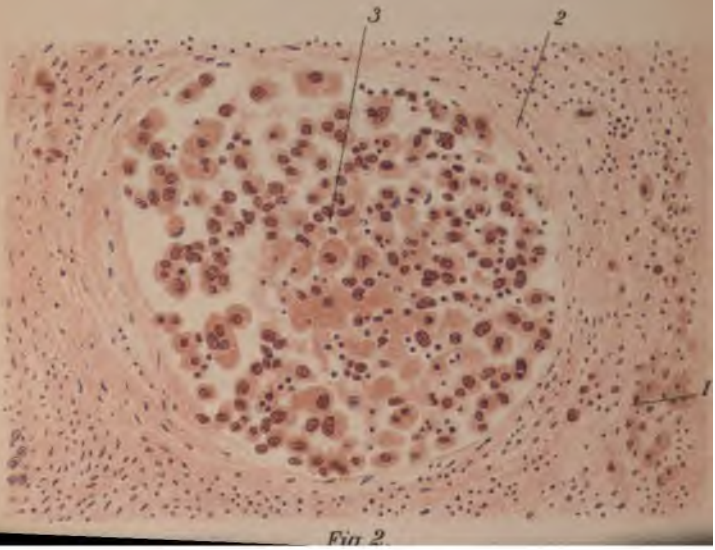

Fig. 2.

Accordingly, carcinomatous emboli are quite frequently found in small pulmonary arteries, and as they first cause coagulation of the blood and disintegration of the corpuscles, they are usually found imbedded in thrombus at the point where they have been arrested (Plate 77, Fig. 1). Carcinomata situated in the area which supplies the portal system quite frequently invade the branches of the portal vein and cause transplantation of tumor-particles to the liver, where they make their way through the vessel-wall and form the germ of metastatic tumors (Plate 77, Figs. 1 and 2).

Microscopic examination of these particles of carcinoma lying within the blood-vessels shows better than anything else that the epithelium is the necessary and essential element in the spread of the tumor; for the tumor emboli which are formed consist almost always exclusively of loose or closely packed epithelial cells without a vestige of stroma, the latter being produced secondarily by the surrounding tissue after the cells had deposited themselves, possibly at first by the proliferation of the endothelial cells of the blood- or lymph-vessels.

The so-called *malignant chorion-tumor*, described by Marchand as *syncytial carcinoma* or *choriocarcinoma*, may be placed side by side with carcinoma. This form of tumor develops from the epithelium of the chorionic villi of the placenta and from Langhans' cells. The syncytium and the Langhans' cells are usually represented about equally in the primary tumors. The growth is often associated with the formation of a cystic (hydatid) mole, a myxomatous degeneration of the chorionic villi, in which proliferation of the villous epithelium is often demonstrable. The principal portion of the tumor consists of irregular, broad and narrow trabeculæ and bands of a continuous mass of protoplasm, pierced by numerous vacuoles, in which the outlines of individual cells are barely discernible. The largest nuclei, which are rich in chromatin, often of irregular shape, are scattered about in the protoplasmic mass in aggregates of varying density. These trabeculæ unite to form a network surrounding alveoli, containing large, pale, vesicular cells with less intensely staining nuclei, which are often in a condition of mitosis, and, judging from their shape and spatial relations to the syncytium, must be regarded as the descendants of Langhans' cells.

These tumors invade the muscular tissue of the uterus and its blood-vessels, and occasionally lead to multiple metastases in the body, particularly in the lungs. In the metastatic tumors the syncytial arrangement is usually less distinctly discernible. The protoplasmic mass is often broken up into shapeless, multinuclear giant-cells, or into smaller, nuclear elements, nor are Langhans' cells so distinct as in the primary tumors.

ENDOTHELIOMA.

The neoplasms known under the name of endothelioma occupy a special position in onkology. They may be said to be intermediate between connective-tissue and epithelial neoplasms. While in a genetic sense they resemble the first group, and have, therefore, frequently been regarded as a subdivision of sarcoma, their morphologic properties are such as to bring them nearer the carcinomatous neoplasms. It is true that both macroscopically and histologically the morphology is, as we shall see, extremely variable; and it is often very difficult in a given case to recognize the endothelial character of the tumor. Accordingly the term *carcinoma sarcomatodes* or *sarcoma carcinomatodes* has been proposed for these difficult transitional forms; but as it is preferable to base the classification of a tumor on histogenetic principles whenever it is possible to do so, we cannot well dispense with the conception of endothelioma, and in a good many instances it is quite possible to trace the origin of the tumor to endothelial cells.

It first becomes necessary to state clearly what kind of cells are to be designated endothelial cells, for in this respect anatomic nomenclature leaves much to be desired in the way of uniformity. Disregarding individual morphologic differences, we apply the term "endothelium" to all those cells, usually of the squamous type, and presenting a mosaic arrangement, which line the blood- and lymph-vessels, the lymph-clefts of the connective tissue, and the serous cavities of the body. Recently many anatomists have also applied the term "epithelium" to these cellular elements, but there are both genetic and pathologic reasons why it is better to make a distinction between them and true epithelial cells; for, in the first place, it has been positively established by recent investigators that all these structures are derived from the intermediate germinal layer (mesoderm), while true epithelium is either an ectodermal or an endodermal formation. Another important reason for grouping together the cells which line the serous cavities of the body is that they are all capable, under pathologic conditions, of furnishing fibroblasts—*i. e.*, cellular elements capable of functionating as the predecessors of connective-tissue cells and of secreting from their protoplasm a collagenous, fibrillar, intercellular substance.

The microscopic picture of endothelioma is extremely variable; it may approach the type of a true epithelioma, either the adenoma or cystadenoma, or a carcinoma; on the other hand, the structure may be so diffuse as to render the distinction from sarcoma, especially alveolar sarcoma, extremely difficult. As the more or less extensive cell-aggregations frequently contain at their centers blood-vessels whose walls are intimately connected with the surrounding cells, this variety of tumor has frequently been designated *angiosarcoma*—*i. e.*, a tumor consisting of vascular and connective tissue, a name that may be justifiable when applied to a tumor having its origin in certain definite cellular constituents of the vessel-wall, which also belong to the connective-tissue group. It would be altogether improper, however, to designate every sarcoma that is abundantly supplied with blood-vessels an angiosarcoma, thus implying a combination of a vascular tumor—*i. e.*, an angioma—with a tumor consisting of connective tissue of a juvenile type—*i. e.*, sarcoma. In order to avoid such ambiguity it seems wise

PLATE 78.

FIG. 1.—**Endothelium of the Pleura** (Hemat.-eosin. × 385.): 1, Thickened pleura; 2, flat cells; 3, polyhedral cells with abundant protoplasm.

FIG. 2.—**Blood-vessel Endothelioma (Perithelioma), with Hyaline Degeneration Cylindroma—from the Jaw** (Hemat.-eosin. × 280.): 1, Surviving endothelium in (2) vessels with hyaline walls; 3, proliferated perithelial cell-masses.

FIGURE XXXIII.

Capillary Endothelioma from the Testicle of Papillary Structure (× 66.): 1, Interlacing tubes of proliferated endothelial cells; 2, cystic cavities lined with endothelium; 3, connective-tissue stroma.

FIGURE XXXIV.

The Preceding Figure in Detail (× 280.): 1, Endothelial cells; 2, cavities surrounded by endothelial cells, some containing blood-cells; 3, scanty connective-tissue stroma.

to eschew the term angiosarcoma and substitute in its place the term *endothelioma*, at the same time accepting the nomenclature which naturally follows from the adoption of that word.

As in the case of vascular tumors of typical structure, neoplasms derived exclusively from endothelial cells may be divided also into those consisting chiefly of endothelium from lymph-vessels or lymph-spaces, and those which originate from the endothelium of blood-vessels. The former would, accordingly, be designated lymph-vessel endothelioma or *lymphangio-endothelioma*, and the latter blood-vessel endothelioma or *hemangio-endothelioma*. As will be shown presently, the latter group must also include tumors which take their origin in endothelial cells which form the lining of perivascular sheaths. Although the latter are chiefly lymphatic in nature, the tumors to which they give rise cannot be separated from their native soil, the blood-vessel wall. These cells are known as perithelial cells, and the tumors to which they give rise are called peritheliomata.

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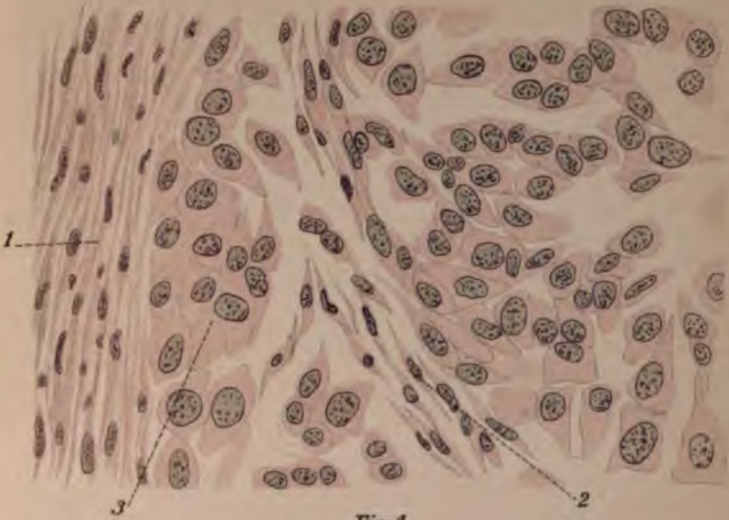

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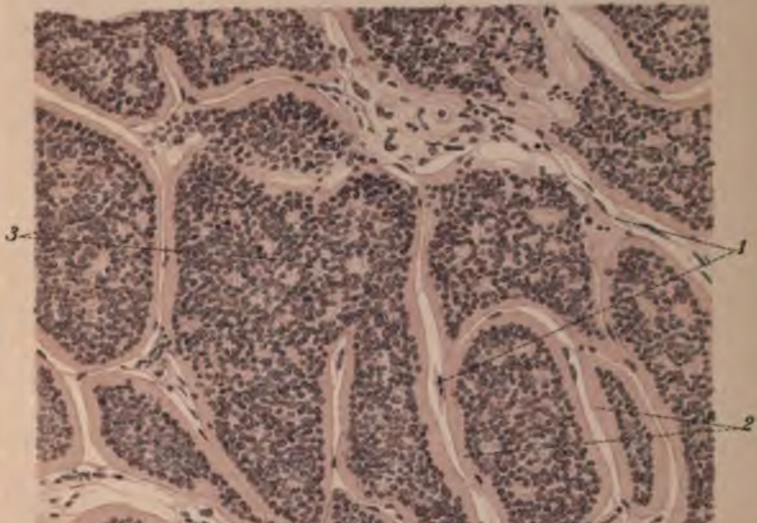

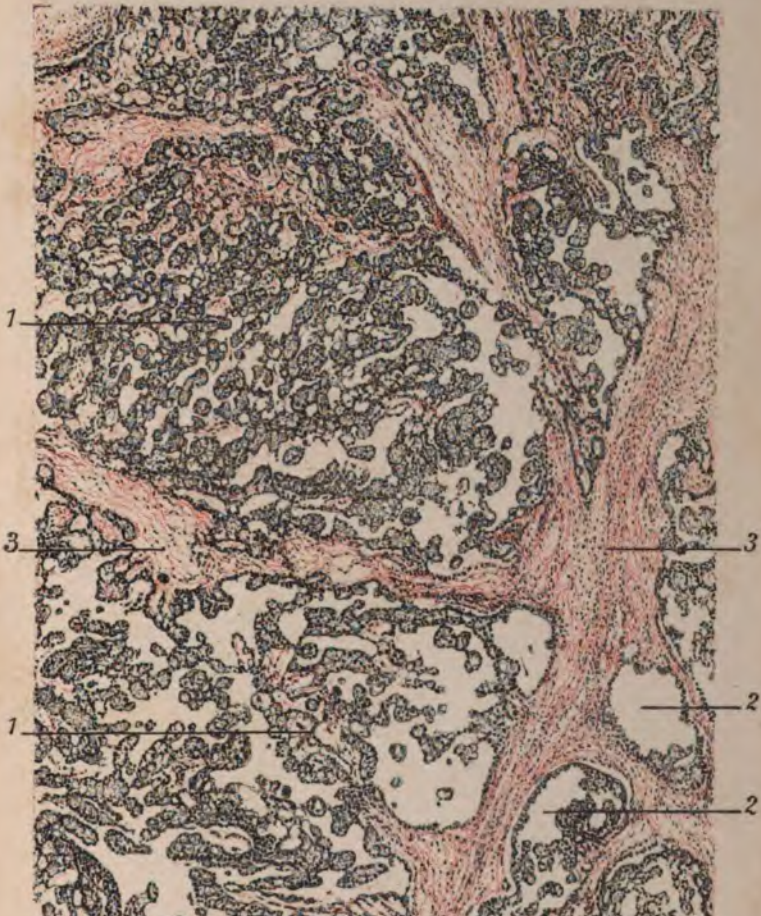
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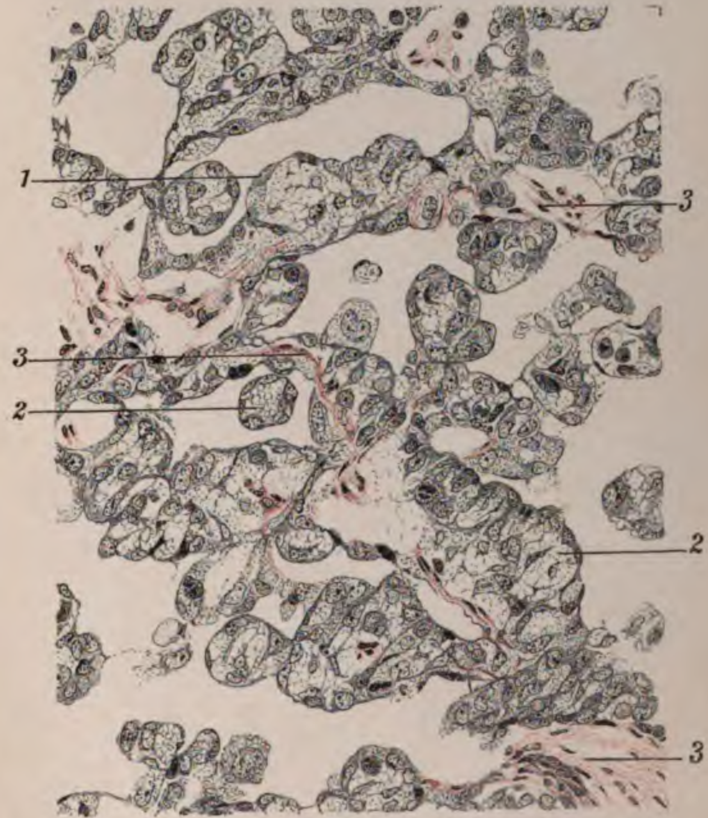


Fig. XXXIV.

A **lymph-vessel endothelioma** is composed in the main of cell-cords consisting of squamous, rhomboidal or spindle-shaped cells in close apposition to one another. These continuous cords and tubes of cells are extremely variable as regards their caliber, and in sections they, of course, exhibit the same alveolar structure as the identically formed epithelial tumors. The cell-cords are accompanied on their outer side by a vascular stroma, the meshes of which are forced apart and infiltrated by the cellular proliferation of the lymphatic endothelium. Sometimes the occlusion of the affected lymphatic vessels, due to the cellular proliferation, is not complete, the growth taking place chiefly in the direction from within outward and leaving tubes and canals lined with several layers of cells. The individual cells of these tubes may experience considerable increase of their protoplasm and enlarge until they form large epithelioid structures. In this way gland-like cell-aggregates are formed which at the first glance strongly suggest the picture of an adenoma, or, if they consist of several layers, the structure of an adenocarcinoma. As a rule, however, the close genetic and morphologic connection between the cells of the tumor-parenchyma and those of the tumor-stroma is shown by the presence of protoplasmic processes, which can be traced from the former into the adjoining stroma, as well as by the presence of the slender intercellular substance, composed of cell-processes, which is occasionally formed between the cells. While, therefore, these tumors are distinctly different from carcinoma in this respect, they, on the other hand, bear a most perplexing resemblance to the type of those tumors which have been described above as alveolar sarcoma. In fact, the classification in a given case may be so difficult that it may be impossible, by the examination of individual particles taken at random from the tumor or from sections of such particles, to decide whether the growth is an alveolar sarcoma or an endothelioma. In such a case it is necessary to study the marginal portions of the tumor, where the flat cells are still found clearly separated from the outer

PLATE 79.

FIG. 1.—**Endothelial Psammoma of the Meninges** (Picro-carmin, × 70.): 1, Fibrous stroma; 2, spheroid, concentrically laminated, calcareous bodies; 3, mulberry-shaped calcareous bodies.

FIG. 2.—**Endothelial Cholesteatoma from the Base of the Brain** (× 220.): 1, Outer layer of cholesteatoma spheres with squamous cells; 2, inner layer, void of nuclei, consisting of attenuated remains of cells.

FIGURE XXXV.

Endothelioma of the Pia Mater (× 180.): 1, Spindle-shaped cells; 2, spheroid masses of cells derived from the former and arranged in concentric layers; 3, spheric masses of cells in hyaline degeneration.

FIGURE XXXVI.

Mixed Tumor from the Parotid Gland (× 80.): 1, Plugs and tubes of cuboidal epithelium; 2, spheric masses of horny, squamous epithelium, arranged in concentric layers; 3, horny masses; 4, myxomatous connective tissue.

connective tissue with which they are contiguous. If the intercellular substance is very sparingly developed, we have the forms for which the above-mentioned terms carcinosarcoma or carcinoma sarcomatodes were invented.

On the other hand, the union with the intercellular substance may be so intimate, the transition from the fibrillar, long-drawn-out cells of the tumor-masses to the surrounding stroma may be so gradual, that the tumor in its general appearance resembles certain cellular forms of fibroma.

Such a tumor is spoken of as an endothelioma with fascicular arrangement. When the cell-tubes are club-shaped and form tangled masses, we have a plexiform endothelioma. In the latter variety of tumor the spindle-shaped cells may be amalgamated in concentrically laminated spheric masses, closely resembling similar epithelial laminated spheres in squamous carcinoma. In these tumors the cells, which are imbricated like the successive layers of an onion, are frequently conglomerated and form

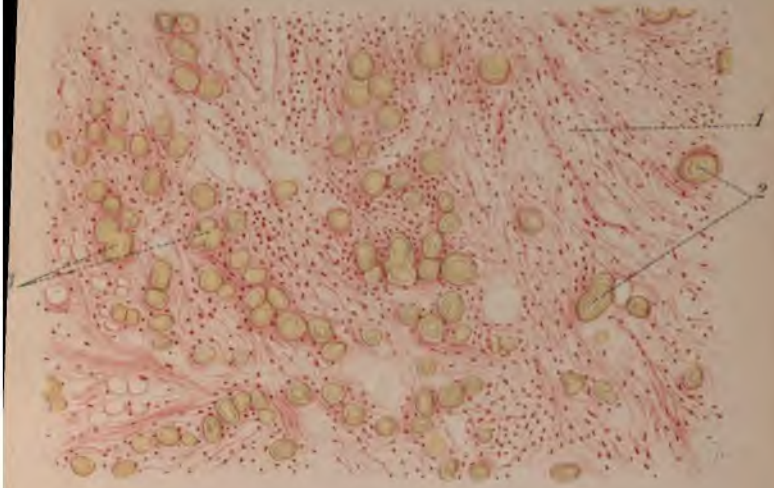
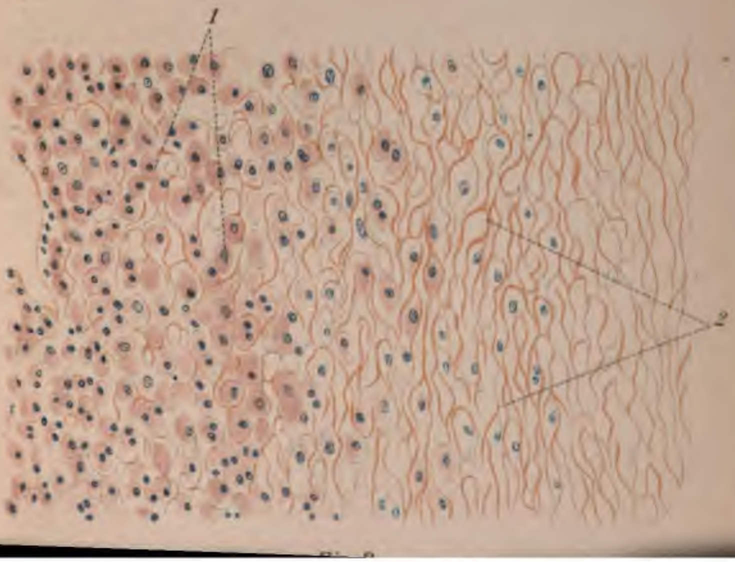


Fig.1.



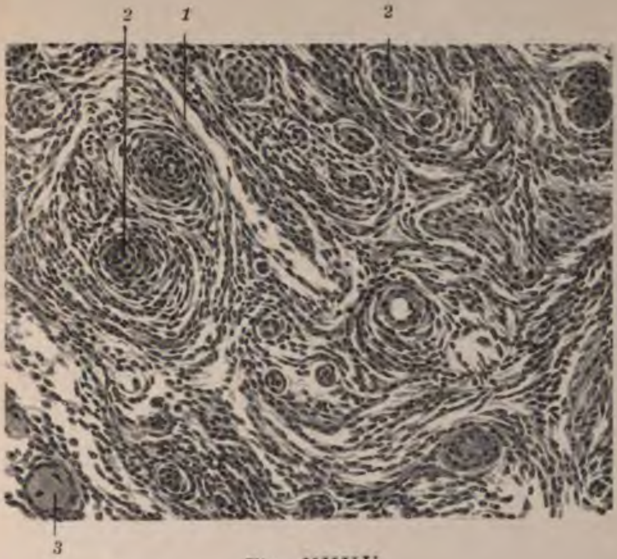
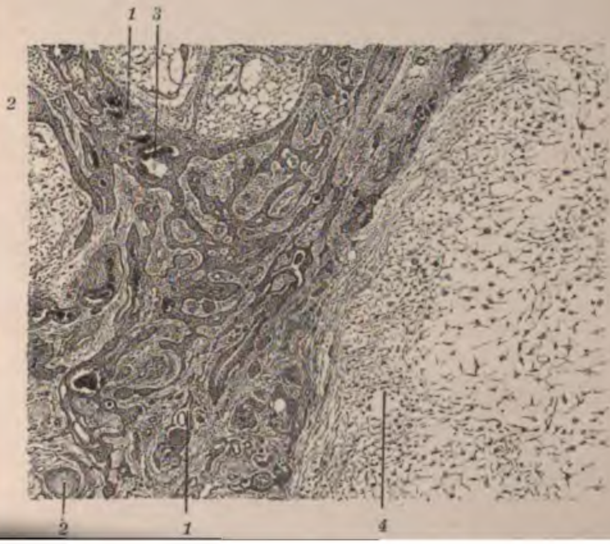


Fig. XXXV.



hyaline spheric masses of homogeneous appearance. In the latter again calcium salts may be deposited, and in this way are formed those peculiar concentrically striated calcareous concretions, either spheroid or mulberry-shaped from the close apposition of the cells, which microscopically exhibit the greatest similarity to the particles of so-called "brain sand" (acervulus cerebri). When the endothelioma has undergone these changes, it is designated a **psammoma.** Tumors of this kind have their seat chiefly in the dura mater and in the soft membranes of the brain. Sometimes the endothelial cell-masses in large areas of the tumor are completely converted into those calcareous spheres of laminated structure, or into cylindric, rod-shaped, or bizarre calcareous masses, with only the scanty remains of fibrous stroma between them. This gives the microscopic picture the appearance as if calcareous concretions had been deposited in a fibroma, and it is only by careful examination, showing that these concretions are formed in the marginal portions of the tumor, that their true origin can be recognized (Plate 79, Fig. 1, and Fig. XXXV.).

Tumors after the type of endothelioma may also grow from the large flat cells lining the serous cavities, which are also to be regarded as endothelial cells. As these cells swell with every proliferative process and assume a cuboidal or almost cylindric shape, the morphology of these tumors even more closely approaches the character of carcinoma, and they have accordingly been described as "*endothelial carcinoma*" of serous membranes in recognition of the endothelial nature of the parent cells (E. Wagner, Schulz). These neoplasms take the form either of a diffuse hard enlargement or of fungous, sessile tumor, with broad bases projecting into the lumen of the serous cavity; as a rule, they exhibit a distinctly alveolar structure. The parenchyma-cells of the tumor, which are sometimes quite large, rich in protoplasm, and either rhomboid or polyhedral in shape, are often in close relation with the surrounding stroma (Plate 78, Fig. 1), and while at the center of the tumor the cells are polygonal and soft, they gradually shade off in the marginal portions of the alveoli into flatter elements, and finally into the narrow, spindle-shaped cells of the surrounding stroma. The interstitial connective tissue may be quite abundant, and may even undergo marked hyperplasia of the fibrous substance, so that the tumor may consist of linear rows of endothelial cells, interpolated between thick masses of fibrous tissue consisting of several layers. In this way is produced that diffuse hard thickening of serous membranes, a condition that is sometimes observed in the entire parietal and visceral peritoneum, for example, and envelops the abdominal organs in a rigid connective-tissue armor—a formation which was formerly described as diffuse fibrosarcomatosis of serous membranes. Similar endothelial tumors with an abundance of stroma also occur in the stomach, especially in the pyloric portion; they are more circumscribed, although they also exhibit a tendency to lateral, superficial extension. This variety unquestionably includes many cases of so-called scirrhus of the pylorus, in which the mucous membrane remains intact and the entire gastric wall presents diffuse thickening, enhanced by the muscular hypertrophy at the pylorus which takes place secondarily. But it has never been proved that these last-mentioned forms originate from the superficial endothelium of serous membranes or from their lymph-vessels.

Blood-vessel endothelioma or hemangio-endothelioma, is the result of proliferation of the endothelium of blood-channels. Large vessels, either arterial or venous, are rarely attacked; but the smaller arteries, particularly the smaller veins that still possess a distinctly recognizable, independent wall, quite frequently represent the starting-point of such tumors. It is therefore desirable to separate these formations from tumors which evidently take their origin solely in proliferation of capillary endothelium, often with the formation of true convolutions of canalized endothelial buds, and to separate true hemangio-endothelioma from tumors which, on microscopic examination, are at once recognized as capillary endotheliomata. The tubular cell-masses produced in this way exhibit definite relations to the blood-vessels, so that these tumors were and still are designated angiosarcoma, a term that may be accepted with the above-mentioned reservations in view of the mesenchymatous (mesodermal) nature of the tumor matrix. Capillary endotheliomata often exhibit a distinctly papillary structure (Figs. XXXIII. and XXXIV.). The massive interlacing tubes of closely aggregated endothelial cells, frequently with a cavity in the interior which may even contain blood, rest on a foundation of fibrous stroma. The endothelial cells are sometimes large, the walls of the tubular structures being sometimes lined with two or three layers of them and sending into the lumen bud-like projections or connecting bridges, in addition to forming a mantle around small capillary cavities. These proliferated cells also penetrate the connective tissue and form the lining of tissue-spaces resembling cysts, which they invest with one or more layers of cells; or they may form fresh papillary projections in their own lumen.

In the same class with blood-vessel endothelioma we have the **perithelioma**—*i. e.*, a tumor having its origin in cells that lie within the adventitia of blood-vessels and is genetically, as well as morphologically, equivalent to endothelial cells. Proliferation of these cells gives rise to tubular cell-masses surrounding the outside of blood-vessels like a mantle and presenting such dense cell-conglomerations that the intervening stroma practically disappears and the tumor seems to consist of interlacing strands and cords of spindle-shaped or polyhedral cells, usually with well-preserved central lumina. These were formerly known as *tubular sarcoma.* The endothelium which lines the interior of the vascular lumen is often well preserved (Plate 55, Figs. 1 and 2; Plate 56, Fig. 1); but the rest of the vessel-wall is completely infiltrated with perithelial cells, and the individual layers cannot be made out. It is needless to say that the tumor-masses may break through into the lumen and cause hemorrhage into the surrounding tumor-tissue, with the formation of blood pigment within the latter, so that the entire tumor-mass may be completely infiltrated with blood-pigment and microscopically present a diffuse, russet-brown discoloration (Plate 55, Figs. 1, 3).

The endothelial elements are frequently the seat of retrogressive metamorphosis, particularly hyaline degeneration, which in such cases always attacks the vessel-wall and leads to the production of homogeneous cylindric masses, often with club-shaped extremities. As the latter in a recent, teased preparation are readily separated from the surrounding cellular material, and then appear as shining homogeneous cylinders, the tumor has often been described as a **cylindroma.** It is obvious that the spatial relations between the hyaline cylinders, which always appear primarily in the vessel-walls themselves, and the cell-aggregates must be different according as it is a true blood-vessel endothelioma or a so-called perithelioma that has been attacked by the process. In the former case hyaline cylinders are formed at the surface of the proliferated masses of endothelium (Plate 56, Fig. 2); in the latter case hyaline tubes are formed which are surrounded on the outside by the proliferated perithelial cells. In the interior of the hyaline cylinders isolated endothelial cells may still be demonstrable (Plate 78, Fig. 2). In cross-sections the hyaline structures appear as spheres or irregular fragments.

To the group of endothelial tumors also belong certain neoplasms which are included among the so-called **cholesteatomata.** The term cholesteatoma, like psammoma, is not intended to describe the nature or origin of the corresponding tumor. It is merely intended to indicate that we have to deal with the formation of shining pearls and the deposition of cholesterin in the tumor. Many cholesteatomata are of an epidermoid nature, but it is evident, from the character of the cells that make up endotheliomata, that they may, under certain circumstances, develop the faculty of producing cell-aggregates presenting an imbricated arrangement like the scales of a fish. As a matter of fact, many of the cholesteatomata which occur in the soft membranes of the brain, and probably all those which have their origin in the choroid plexus, may, on histogenetic grounds, be assigned to the domain of endothelioma. These tumors are spheric or may be composed of confluent masses and exhibit the well-known silky or mother-of-pearl sheen; they are extremely hard, and of a dry, friable structure. On microscopic examination the inner portions of these conglomerations are found to consist of small imbricated scales without nuclei, while the outer portions still reveal large, densely packed vesicular cells with distinct nuclei. They originate in the endothelium of the subarachnoid spaces or in the lymph-vessels of the plexuses (choroidal plexuses).

These cholesteatomata, on the other hand, which grow from the base of the brain toward the cerebrum, and which are attributed to the inclusion of epidermoid tissue-rests, usually in the region of the sella turcica, have quite a different origin. Of course, the so-called cholesteatomata of the middle ear consist solely of cells from the epidermis, and hence must not be included among the endothelial cholesteatomata. They are frequently due to chronic inflammatory processes, with invagination of epidermal tissue into the middle ear, or to metaplastic processes in the epithelium of the mucous membrane. Sometimes they may represent large conglomerations of cells which erode the bone, and on microscopic examination present a concentric laminated structure, some of the constituent epithelial cells possessing nuclei and some being devoid of them. The so-called cholesteatoma of the urinary passages, which is observed in the pelvis of the kidney, in the ureters, and in the urinary bladder, has a similar origin. It is probable that these tumors owe their existence exclusively to metaplastic processes in the epithelium, which in turn are excited and maintained by chronic inflammatory processes. In this way whitish sessile excrescences with a broad base and ragged surface resembling a cock's comb may be formed on the corresponding mucous membranes; on microscopic examination they are found to be made up almost exclusively of stratified squamous epithelium in concentric layers, sometimes in a state of partial cornification.

MIXED TUMORS AND TERATOID GROWTHS.

The term mixed tumors is used to describe neoplasms in which several kinds of tissue are represented, not only in the sense that they bear the relation of tumor-stroma and tumor-parenchyma to one another, but also in the sense that the parenchyma itself may consist of a combination of different kinds of tissue, in which case the presence of a vascular stroma is indispensable. The possible combinations of different kinds of tissue are very numerous, and the individual varieties may be genetically very different from one another. Since, however, the simultaneous production of several, genetically quite distinct tissues from a single ground-tissue is inconceivable, and in many cases cannot be explained by metaplasia, mixed tumors have always been attributed to the inclusion of fetal germs. Cohnheim's theory of the etiology of tumors accordingly applies in its fullest sense to these types. Recently it has been thought (Wilms) that these mixed tumors originate in germs that have been extruded from the community of tissues at various stages of fetal development, have later proliferated, and, since they consisted of indifferent structural material, have undergone differentiation in various directions; in other words, have undergone the same differentiation-processes in postfetal life as normally belong only to fetal tissues. The earlier this exclusion of cell-complexes takes place, the greater the subsequent power of these germs to develop and undergo differentiation. Cell-complexes derived, for example, from the first segmentation-spheres may be extruded at a very early period, and may, under certain circumstances, develop into tumors of complex composition, which can be attributed only to a germ-layer, and which are called **teratomata** or **teratoid tumors.**[1]

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[1] This class of tumors was formerly, as a rule, attributed to the fusion of two separate embryos, with the early destruction of one by inclusion in the other.

If the process of differentiation goes so far as to form the actual organs of the embryo, the term "*embryoma*,"which was introduced by Wilms, may be quite appropriate. Not to be included in the same category with the mixed tumors are those formations which, beyond a doubt, are due to double embryos with cohesion; these may be designated *bigerminal teratomata*.

True mixed tumors, in the narrowest sense of the term, occur chiefly in the kidney, the urinary bladder, the cervix uteri, vas deferens, and mammary gland; also in the salivary glands (parotid and submaxillary), in the orbits, and in the palate. They may represent a variously compounded mixture of more or less differentiated tissues or tissue-germs. As regards their quantitative distribution also, great differences obtain. During the evolution of these germs into tumors, which almost always represent preëxisting structures, the indifferent embryonal structural tissue of mesenchymal origin, as a rule, greatly predominates; hence these neoplasms have often been classified among the sarcoma. The remaining tissue-elements in the growth, which could not be made to fit in with the sarcoma type, are either disregarded altogether or furnish the other part of the name. Accordingly the older nomenclature of these tumors is extremely complicated, and contains such terms as carcinosarcoma, or myosarcoma carcinomatodes, etc.

In the kidney, where mixed tumors are frequent, especially during childhood, the tumors contain, in addition to indifferent formative cells which have enormously proliferated and assumed a malignant, sarcomatous character, the muscle-tissue of the same immature variety as is found in rhabdomyoma and rhabdomyosarcoma; smooth muscle-fibers and occasionally cartilaginous or osteoid substance may be found scattered through the tumor. In addition, there may be epithelial formations, glandular tubes, or solid epithelial nests and plugs, surrounded by sarcoma-like masses. Sometimes a distinct membrana propria is present. Metastatic growths derived from these tumors, which are clinically often malignant, and therefore, were

PLATE 80.

FIG. 1.—**Teratoma from the Perineum (Teratoid Sacral Tumor)** (Hemat.-eosin. × 30.): 1, Connective-tissue stroma; 2, cysts lined with cylindric epithelium; 3, glandular collections of epithelial cells; 4, transversely striated muscle-fibers; 5, islands of cartilage.

FIG. 2.—**Teratoid Sacral Tumor** (Hemat.-eosin. × 70.): 1, Connective-tissue stroma; 2, stratified, squamous epithelium; 3, tall, cylindric epithelium; 4, cuboidal epithelium; 5, gland-tubes.

formerly described quite often as carcinomata, also present the same structure as the primary tumor; or they may consist of indifferent, cellular, formative tissue, in which case they give the impression of a round-cell or polymorphocellular sarcoma.

Identical tumors also sometimes develop in the cervix uteri and vagina. In the mammary gland there may be, in addition to the tubular masses of epithelium, scattered masses of squamous epithelium with cornified layers, or masses of mucoid and of osteoid tissue. The salivary glands present a particularly rich soil for tumors of this kind, in which connective-tissue germs in all stages of differentiation—aggregations of round- and of spindle-cells, mucous tissue, fat-lobules, cartilaginous and bony tissue—are observed, with scattered islands of epithelial tubes containing either one or several layers of epithelium. Sometimes the shape of the cells that make up these tubular aggregates or their relation to the surrounding tissue gives the impression of an endothelial origin.

Among this group of tumors, which are to be attributed to developmental disturbances, should be included a series of cystic formations which either reproduce in their walls the structure of the outer skin, and are then designated **dermoid cysts**, or correspond to the structure of the mucous membrane of the respiratory or digestive tract, and are then known as *enterocysts*. Finally, these cystic formations may develop from persisting remains of branchial pouches; such structures are known as *branchial cysts*.

The wall of a dermoid cyst usually consists of a fibrous,

Tab. 80.

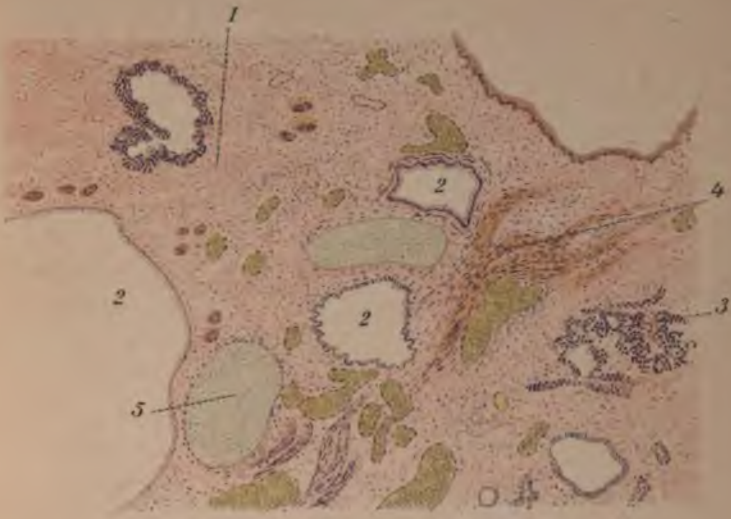
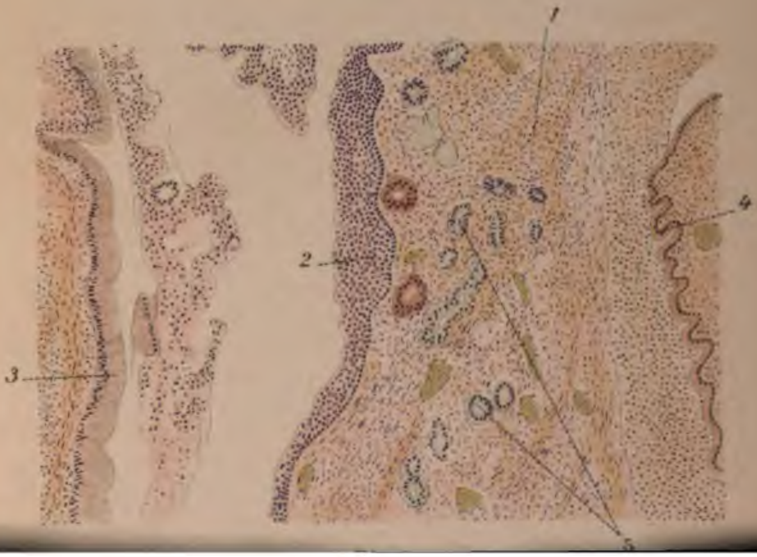


Fig. 1.



connective-tissue envelop with an internal lining of stratified, squamous epithelium after the type of the epidermis situated on papillary elevations. Cutaneous glands and hair may also be present. As a result of desquamation of epidermal cells and horny scales and the falling-out of hairs, the lumen may be filled with a heterogeneous material, sometimes mixed with masses of fat and cholesterin. These dermoid cysts are due, as a rule, to dislocation of fetal tissue. They occur in the skin and subcutaneous tissue, in the cranial cavity, and in the vertebral canal, on the neck, in the mediastinum, and occasionally in the abdomen.

Not to be confounded with these dermoid cysts are the simple **epidermoids**, the inner lining of which consists solely of squamous epithelium without any structures derived from cutaneous appendages. It has already been pointed out that these epidermoids, by proliferation of the epithelial cells and their arrangement in concentric layers to form pearly structures, furnish part of the tumors known as cholesteatomata. This group also includes the so-called *traumatic epithelial cysts*, which owe their origin to the dislocation of portions of the epidermis into the subjacent connective tissue, with subsequent proliferation of the former.

Spurious tumors that are sometimes confounded with dermoids or epidermoids are the so-called **sebaceous cysts.** They belong to the so-called retention-cysts, and are formed by the occlusion of the ducts of sebaceous glands. The dilated glands surround themselves with a dense connective-tissue membrane, the inner surface of which is usually lined with squamous epithelium. The cavity of these pseudotumors contains sebum, fat, cholesterin, etc., which make up the sebaceous material.

Cysts lined with mucous membrane (enterocysts) are found in the oropharyngeal cavity, in the wall of the esophagus, in various portions of the abdominal walls, and even in the liver.

Branchiogenic cysts owe their origin to the remains of branchial pouches and of branchial arches in the neck.

They also consist of a connective-tissue capsule, and are lined with squamous, or more frequently with cylindric or ciliated, epithelium, from which crypts may dip down into the depths of the tissue. The connective-tissue wall frequently contains follicular collections of leukocytes, and sometimes, in addition, scattered masses of cartilage which are probably derived from persistent rests of the branchial arches.

True teratomata, or **teratoid tumors,** have their seat in the sexual glands, or at the posterior or anterior poles of the trunk, appearing either as sacral tumors or as teratoid pharyngeal polypi. Their histology is extremely complex, and can be explained only by supposing the dislocation of a mass consisting of the three germinal layers at a correspondingly early embryonal period. The simplest structures of this kind occur in the testicle, where they usually consist of embryonal connective tissue with scattered islands of cartilage and epithelial cell-aggregates, composed partly of squamous epithelium, with cornification, and partly of cylindric epithelium. Teratoma of the ovaries often exhibits a much more advanced differentiation, the mesodermal portion of the tumor being often so perfectly differentiated that true skeletal parts are produced. In addition to cartilage there may be found bones, sometimes with articular surfaces, jaw-like structures with an alveolar margin, enamel-cells, enamel-pulp, and well-developed dental papillæ, besides epidermoid structures of the character of dermoid cysts and filled with desquamated epithelium, sebaceous masses, hair, etc.

The identical histologic composition may be observed in teratoma developing at either end of the trunk. Sacral tumors, which are often quite large, usually consist partly of a cystic and partly of a solid portion. They are supported by a cellular connective tissue, which in many places is myxomatous and contains scattered masses of cartilaginous and bony tissue (Plate 80, Figs. 1 and 2). In addition they contain muscle-fibers, with or without transverse striation, nerves, extensive fragments that look like tissue from the central nervous system, with well-developed neuroglia and ganglion-cells. The epithelial structures may present every variety and form of epithelium. There are cysts and tubular cavities lined partly with cylindric, and partly with stratified, squamous epithelium. Sometimes the same canal is lined on one side with cylindric or ciliated, and on the opposite side with stratified, squamous epithelium. Every imaginable kind of glandular structure may be observed. Sometimes there are found scattered through the tumor-cell masses or cystic cavities containing polyhedral epithelium densely packed with dark pigment-granules, resulting in formations of the type of the pigmented epithelium of the retina—so-called *eye-dots.*

The tumors which grow at the anterior pole of the trunk in the form of pharyngeal polypi exhibit a similar composition. Their surface is often covered with hair (*hirsute pharyngeal polyp*), and they may communicate with similar tumors in the cranial cavity by means of bridges that traverse the skull. They may also harbor, in addition to a mixture of tissues derived from the three germinal layers, fully differentiated organs, structures resembling the extremities of the body, glands, teeth, etc. All these tumors may be summed up under the name *embryoma.*

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Substitute for Clinical Observation

As an indication of the great practical value of the atlases and of the immense favor with which they have been received, it should be noted that the **Medical Department of the U. S. Army** has adopted the "Atlas of Operative Surgery" as its standard, and has ordered the book in large quantities for distribution to the various regiments and army posts.

Adopted by U. S. Army

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